Janssen Research & Development *
Final Synoptic Clinical Study Report: Report of Long-term Extension

A Phase 3, Randomized, Open-label Study of Subcutaneous and Intravenous VELCADE® in Combination with Dexamethasone in Chinese Subjects with Relapsed or Refractory Multiple Myeloma

Protocol 26866138MMY3037; Phase 3

JNJ-26866138-AAA (bortezomib)

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VELCADE is the exclusive trademark of Millennium Pharmaceuticals, Inc., registered in the United States and internationally.
VELCADE intravenous administration is approved for marketing in China for 3 indications: naive multiple myeloma, relapsed multiple myeloma, and relapsed mantle cell lymphoma. VELCADE subcutaneous administration has been approved for marketing authorization in China on 21 August 2018.

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Protocol No.: 26866138MMY3037

Title of Study: A Phase 3, Randomized, Open-label Study of Subcutaneous and Intravenous VELCADE® in Combination with Dexamethasone in Chinese Subjects with Relapsed or Refractory Multiple Myeloma

Name of Active Ingredient(s): JNJ-26866138-AAA (bortezomib)

NCT No.: NCT02811978

Clinical Registry No.: CR108175

Coordinating Investigator(s): Jian Hou, MD, PhD

Study Center(s): This Clinical Study Report (CSR) summarizes the results from the 17 study sites located in China that enrolled subjects.

Publication (Reference): None.

Study Period: 29 September 2016 (Date of first subject signed informed consent) to 10 November 2018 (Date of 1 year after randomization of the final subject)

Phase of Development: 3

INTRODUCTION:

This document presents results of the Study 26866138MMY3037 (Study MMY3037) long-term extension: pre-planned analyses with a data cutoff date of 1 year after randomization of the final subject on 10 November 2017. At the data cutoff date of 07 May 2018 for the primary Clinical Study Report (CSR), 52 subjects were still in the study, 2 of whom were still receiving V(SC)d therapy.[2] The long-term extension analyses utilized a data cutoff date of 10 November 2018, meaning 6 months of additional follow-up for the analysis on long-term endpoints of overall response rate (ORR) at the end of 8 cycles, progression-free survival (PFS), 1-year survival rate, time to progression (TTP), time to response/best response, duration of response, all-cause mortality, and other safety update.

Study MMY3037 was a randomized, open-label, Phase 3 study conducted at multiple sites in China to evaluate the efficacy of VELCADE SC as compared with VELCADE IV when administered in combination with low-dose dexamethasone in adult Chinese relapsed or refractory multiple myeloma (r/rMM) subjects. The study consisted of 3 phases: a 3-week (21-day) screening phase, a 24-week open-label treatment phase, and a post-treatment follow-up phase. At least 60 eligible subjects in total would be randomized in a 1:1 ratio to receive VELCADE SC along with dexamethasone (V[SC]d) or VELCADE IV along with dexamethasone (V[IV]d). The study population consisted of adults diagnosed with multiple myeloma (MM), who had received 1 to 3 prior lines of therapy and had measurable disease and evidence of progressive disease/disease progression (PD) since their last prior therapy.

A pharmacokinetics (PK) assessment part of the study which described the plasma PK following SC and IV administration of VELCADE in a subset of patients (participants in the PK assessment part at select sites), together with initial safety and efficacy part, was reported earlier to support the conditional approval.[1] Data up to the clinical cut-off (CCO) date for primary analysis (07 May 2018) have been summarized in a primary CSR.[2] Key conclusions for Study MMY3037, as present in the primary CSR, include:

- VELCADE SC demonstrated comparable efficacy as compared to VELCADE IV when combined with dexamethasone, as supported by the predefined analyses of primary and secondary endpoints. As the median duration of follow-up for assessment of efficacy was approximately 9.0 months, the estimated 1-year survival rate might not be mature enough.

- The safety profile of V(SC)d was generally comparable to V(IV)d with no new or unexpected side effects. Important differences which favored the SC group were observed, including a lower incidence of treatment-emergent peripheral neuropathy (PN) (24.0%) compared to IV group.
- Total systemic exposure (AUC_{last}) of VELCADE (measured in the form of biologically active bortezomib) was comparable following SC and IV routes of administration.
- In addition, SC administration had acceptable local tolerability.

OBJECTIVES:

Primary Objective: To compare the efficacy of subcutaneous (SC) administered VELCADE to intravenous (IV) administered VELCADE in terms of ORR (complete response [CR]+ very good partial response [VGPR]+ partial response [PR]) after 4 Cycles of treatment, when combined with dexamethasone in Chinese subjects with r/rMM.

Secondary Objectives:

- To evaluate clinical outcomes including CR, and VGPR rates after 4 Cycles of VELCADE (IV or SC) plus dexamethasone (Vd) treatment, ORR after 8 Cycles of Vd treatment.
- To evaluate PFS, 1-year survival rate, time to response, TTP and duration of response (DOR) following Vd treatment, administered either SC or IV.
- To evaluate time to best response following Vd treatment, administered either SC or IV.
- To evaluate safety and tolerability of the 2 routes of administration, including the local tolerability of SC injection.
- To describe the plasma pharmacokinetics (PK) of SC and IV administered VELCADE.

Exploratory Objective: To collect medical resource utilization (MRU) data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this study).

Study MMY3037 showed that the SC route provides an alternate means of administration for VELCADE at the 1.3 mg/m^2 dose without loss of safety or efficacy as compared with IV administration, when combined with dexamethasone. The primary study analysis as presented in the CSR[2] incorporates complete information for the primary endpoint of ORR after 4 cycles, mature information for all secondary efficacy endpoints other than ORR at the end of 8 cycles, 1-year survival rate, and complete safety data for 8 cycles of VELCADE per label.

The pre-planned updated analyses presented within this document, representing the long-term extension of Study MMY3037, utilized a data cutoff date of 10 November 2018 (last subject randomized [10 November 2017] plus 1 year). The main purpose of the update was to provide complete information for the ORR at the end of 8 cycles and 1-year survival rate, two secondary efficacy endpoints. Also evaluated were some time-to-event endpoints, and limited safety data including all-cause mortality.

METHODS:

Study Population:

The study population consisted of adult subjects (aged 18 years or above) diagnosed with MM, who had received 1 to 3 prior lines of therapy and had measurable evidence of PD since their last prior therapy. Subjects should also have achieved a response (PR or better based on investigator's determination of response by the International Myeloma Working Group [IMWG] criteria) to at least 1 prior regimen in the past and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.

The complete list of inclusion criteria and exclusion criteria is available in the study protocol (Appendix 1).

Study Treatment, Dose, Mode of Administration and Batch No.:

Subjects would receive a 1.3 mg/m^2/dose of VELCADE, SC or IV, on Days 1, 4, 8, and 11 of each 3-week treatment cycle.

Dexamethasone would be administered at a dose of 20 mg per oral (PO) on the day of and the day after VELCADE dosing (Days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle).

Details of "study treatments" dosage and administration are available in study protocol (Appendix 1).

All VELCADE and dexamethasone used in the study was provided by the Sponsor through a central supply. There were no updated data about lot numbers and expiration dates for both study drugs from the CCO date for primary analysis to the CCO date for final analysis.

Criteria for Evaluation:

Efficacy

During the study, investigators would assess tumor response and PD in accordance with the IMWG response criteria (refer to study protocol, Appendix 1). Response was confirmed on at least 2 consecutive measurements. Efficacy evaluations would include measurement of myeloma protein in serum and urine, serum calcium corrected for albumin, albumin and β2-microglobulin, bone marrow examination, assessment of lytic disease, and documentation of extramedullary plasmacytomas.

Safety

Safety evaluations would be based on the observation or report of any adverse events (AEs) (including laboratory abnormalities reported as AEs) from the signing of informed consent to the 30 days after the last dose of study treatment. The intensity (severity) of AEs would be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Other study safety evaluations included: local injection site tolerability, neurotoxicity, clinical laboratory tests, electrocardiogram (ECG), Chest X-ray, echocardiogram, vital signs, physical examinations, and ECOG performance status. The timing of all safety procedures is described in the study protocol (Appendix 1).

Statistical Methods for Long-term Extension:

Full details of the statistical analyses that were planned are presented in the statistical analysis plan (SAP).

There was no formal statistical hypothesis to be tested for this long-term extension update. Descriptive analyses were conducted. Additional statistical analyses (e.g. confidence intervals [CIs]) was performed in an exploratory fashion to support the interpretation of overall results. Unless otherwise specified, the analytical approach for the MMY3037 long-term extension was the same as that presented in the SAP for the Study MMY3037 primary CSR.[2]

Populations Analyzed

The following analysis sets were used based on the types of analyses:

- Intent-to-treat (ITT) population was defined as subjects who had been randomly assigned to the V(IV)d or V(SC)d group. Analyses of subject disposition, demographics, baseline characteristic, ORR, rate of VGPR or better and time-to-event variables were based on this population.

- Response-evaluable population was defined as subjects who had a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening visit. In addition, subjects must have received at least 1 administration of study treatment and have adequate post-baseline disease assessment prior to the start of subsequent therapy. This population was used as sensitivity analyses for selective response-related endpoints.
- Safety population was defined as subjects who received at least 1 dose of study drug (partial or complete). This population was used for all safety analyses. The safety analyses grouping was based on treatment actually received.

Pharmacokinetics

No plan for PK analysis in this long-term extension.

Efficacy

A validated computerized algorithm, which was based on the IMWG response criteria, was primarily used to determine response and disease progression for each subject in the analyses. The algorithm included determinations for the following efficacy-related factors: first response, best response, time to first response, time to best response, duration of response, PD, date of censoring and reason for PD.

For the analysis of ORR at the end of 8 cycles, the 95% CI for the difference in rates (SC - IV) was based on normal approximation. A stratified Mantel-Haenszel estimate of the common relative risk of achieving response and its 95% CI were calculated for the SC arm versus the IV arm.

The distribution of PFS was estimated for each treatment group by the Kaplan-Meier method. Hazard ratio and its 95% CI were estimated based on a Cox's model stratified by ISS staging and number of prior lines of therapy. Analysis methods for TTP were similar to those used for PFS.

The distribution of overall survival was estimated for each treatment group by the Kaplan-Meier method. One-year survival rates based on the Kaplan-Meier estimates were determined for each treatment group.

For responders in each treatment group from ITT population, time to response/best response and duration of response were summarized descriptively using the Kaplan-Meier method. No inferential statistics were provided.

Safety

Treatment-emergent adverse events (TEAEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (Version 20.0) and graded according to NCI-CTCAE version 4.03. Adverse events were summarized by system organ class (SOC) and preferred term, and were presented by treatment groups for safety population. The safety parameters to be evaluated for the long-term extension included the incidence, severity, and relationship to study drug of TEAEs, local tolerability of VELCADE administration, treatment-emergent peripheral neuropathy, clinical laboratory tests and death information.

RESULTS:

SUBJECT AND TREATMENT INFORMATION:

Subject Disposition and Study Completion/Withdrawal Information:

At the time of the 07 May 2018 data cutoff for the primary CSR, 28 subjects in the V(IV)d treatment group and 24 subjects in the V(SC)d treatment group were still in the study, and 2 of the 24 subjects in the V(SC)d treatment group were still ongoing treatment.

81 subjects (40 in V[IV]d group and 41 in V[SC]d group) across 17 sites in China were randomized and constituted the ITT population, and 79 subjects (39 in V[IV]d and 40 in V[SC]d) received at least 1 dose

of study treatment (VELCADE or dexamethasone) and represented the safety population. The response-evaluable population comprised 76 subjects (38 in each group).

As of the cutoff date 10 November 2018 for the final analysis, all subjects had completed or discontinued treatment. As presented in Table 1, for study treatment, the only change versus the disposition results reported in the primary analysis was the re-categorization of 2 subjects in the V(SC)d treatment group from 'subjects who were still on treatment by clinical cutoff' to 'subjects who completed treatment'. A total number of 10 (25.6%) subjects in V(IV)d group and 16 (40.0%) in V(SC)d group completed the 8-cycle treatment. The percentages of subjects who discontinued treatment or discontinued for reasons, including AE, PD, non-compliance with study drug, withdrawal by subject, or physician decision at the final analysis were identical to the primary analysis.

As of the final analysis, all subjects had completed or discontinued study, thirty-five (43.2%) subjects (17 [42.5%] subjects in V[IV]d and 18 [43.9%] subjects in V[SC]d) completed the study and 46 (56.8%) subjects (23 [57.5%] subjects in V[IV]d and 23 [56.1%] subjects in V[SC]d) discontinued the study. The percentages of subjects who completed study or discontinued study remained comparable between the treatment groups at the final analysis. The most common reason for study discontinuation was withdrawal by subject (9 [22.5%] in V[IV]d and 11 [26.8%] in V[SC]d), followed by death (5 [12.5%] in V[IV]d and 10 [24.4%] in V[SC]d) and physician decision in (7 [17.5%] in V[IV]d and 1 [2.4%] in V[SC]d). A number of 11.9% difference (changed from 7.1% difference in the primary analysis) between the two treatment groups in death leading to study discontinuation is observed in the final analysis since more subjects in V(SC)d group died during the long-term extension compared with V(IV)d group. Considering the 15.1% difference between treatment groups in physician decision to discontinue the study, an overview of the 8 subjects is summarized below:

Subject [redacted] in V(SC)d, and Subjects [redacted] in V(IV)d: Since the patient has completed the medication, the investigator's recommended other treatments based on the patient's condition.

Subject [redacted] in V(IV)d: End of study reason is physician decision – PD.

Subject [redacted] in V(IV)d: The investigator believes that the subjects may benefit from other clinical studies if applicable, and that if the subject participates in other study, it may affect the data or purpose of this study.

Table 1: Summary of Subject Disposition; Intent-to-treat Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)	V(SC)d n (%)	Total n (%)
Analysis set: intent-to-treat	40	41	81
Subjects randomized but not treated [a]	1 (2.5%)	1 (2.4%)	2 (2.5%)
Subjects treated [a]	39 (97.5%)	40 (97.6%)	79 (97.5%)
Subjects who completed treatment [b]	10 (25.6%)	16 (40.0%)	26 (32.9%)
Subjects who discontinued treatment [b]	29 (74.4%)	24 (60.0%)	53 (67.1%)
Reason for discontinuation [b]			
Adverse event	12 (30.8%)	10 (25.0%)	22 (27.8%)
Progressive disease	8 (20.5%)	9 (22.5%)	17 (21.5%)
Non-compliance with study drug [c]	8 (20.5%)	2 (5.0%)	10 (12.7%)
Withdrawal by subject	0	3 (7.5%)	3 (3.8%)
Physician decision	1 (2.6%)	0	1 (1.3%)
Subjects who completed study [a]	17 (42.5%)	18 (43.9%)	35 (43.2%)
Subjects who discontinued study [a]	23 (57.5%)	23 (56.1%)	46 (56.8%)
Reason for discontinuation [a]			
Withdrawal by subject	9 (22.5%)	11 (26.8%)	20 (24.7%)
Death	5 (12.5%)	10 (24.4%)	15 (18.5%)

Table 1: Summary of Subject Disposition; Intent-to-treat Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)	V(SC)d n (%)	Total n (%)
Physician decision	7 (17.5%)	1 (2.4%)	8 (9.9%)
Other	2 (5.0%)	1 (2.4%)	3 (3.7%)

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone.
[a] Percentages are based on number of subjects randomized.
[b] Percentages are based on number of subjects treated.
[c] Based on reason 'Subject refused further study treatment' on 'Treatment Disposition' CRF page
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The median duration of follow-up for the total ITT population increased by approximately 7 months from 8.97 months in the primary analysis to 15.97 months in the final analysis (Table 2).

Table 2: Summary of Study Duration of Follow-up; Intent-to-treat Analysis Set (Study 26866138MMY3037)

	V(IV)d	V(SC)d	Total
Analysis set: intent-to-treat	40	41	81
Duration of follow-up (months)			
N	40	41	81
Mean (SD)	12.54 (6.530)	11.28 (7.175)	11.90 (6.851)
Median[a]	15.97	15.34	15.97
Range	(0.3; 23.7)	(0.1; 24.1)	(0.1; 24.1)

Key: V(IV)d = bortezomib (IV infusion)-dexamethasone; V(SC)d = bortezomib (SC infusion)-dexamethasone
[a] Based on Kaplan-Meier product limit estimate.
Note: Duration of follow-up is relative to the date of randomization.
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Demographic and Baseline Characteristics:

The demographic and baseline characteristics of the 81 randomized subjects are summarized in Section 4.2 of the primary CSR.

Demographics and baseline disease characteristics were similar for the V(SC)d and V(IV)d treatment groups, with the exception of age category ⩾65 (22.5% V[IV]d vs. 41.5% V[SC]d) for demographics; percentage of subjects with IgA type of myeloma (10.0% V[IV]d vs. 29.3% V[SC]d), >30% plasma cells by bone marrow biopsy/aspirate test (12.8% V[IV]d vs. 32.5% V[SC]d), and high cytogenetic risk (11.1% V[IV]d vs. 30.8% V[SC]d) for baseline disease characteristics.

Medical History

There were no updated data about medical history from the CCO date for primary analysis to the CCO date for final analysis. Refer to the Section 4.2.3 of the primary CSR.

Baseline Laboratory Values:

There were no updated data about baseline laboratory values from the CCO date for primary analysis to the CCO date for final analysis. Refer to the Section 4.3 of the primary CSR.

Prior and Concomitant Therapies:

Prior therapies of the 81 randomized subjects are summarized in Section 4.4 of the primary CSR. As required by the protocol, all subjects received prior systemic therapies and were VELCADE naive. The number of prior lines of therapy (a stratification factor) was well balanced between the 2 treatment

groups, with the exception of prior autologous stem cell transplant (17.0% in V[IV]d vs. 0 in V[SC]d) and prior cancer-related surgery (20.0% V[IV]d vs. 4.9% V[SC]d).

All subject in the safety population received 1 or more concomitant medications during the study. Similar to the primary analysis, the most frequently reported therapeutic classes of concomitant medications were drugs for acid related disorders, unspecified herbal and traditional medicine, antibacterials for systemic use, blood substitutes and perfusion solutions, mineral supplements, antivirals for systemic use, antianemic preparations, and drugs for treatment of bone diseases (Attachment TSICM02).

After confirmed PD, subsequent antimyeloma therapy was at the investigator's discretion. In the V(IV)d and V(SC)d groups, 12 (30.0%) and 16 (39.0%) subjects, respectively, received subsequent anticancer therapies (Attachment TSISAT01).

Protocol Deviations:

No new protocol deviations were reported during the long-term extension period from the primary CSR. They were summarized in Attachment TSIDEM06.

Treatment Compliance:

The medication compliance, defined as the ratio of total actually received dose and total prescribed dose, were unchanged for V(IV)d group versus the primary CSR. For V(SC)d group, the results changed very slightly because 2 subjects were still receiving treatment at the data cutoff date of 07 May 2018 for the primary CSR. The updated medication compliance for VELCADE and dexamethasone are summarized in Attachment TSIEXP03A. The results indicate that both V(SC)d and V(IV)d treatment groups have good and comparable medication compliance.

Extent of Exposure:

Extent of exposure at the final analysis was similar to the primary analysis and well balanced between the 2 treatment groups.

Duration of Exposure and Relative Dose Intensity

A summary of treatment cycles is presented in Table 3. For the V(SC)d treatment group, any changes in the study treatment finding versus the primary CSR reflect the 2 ongoing treatment subjects at the primary data cutoff of 07 May 2018. As no subjects in the V(IV)d treatment group were ongoing at the primary data cutoff, results for this group were unchanged versus the primary CSR. The median number of treatment Cycles (1 cycle=21 days) was 5.0 for V(IV)d group and 6.0 for V(SC)d group.

Table 3: Summary of Treatment Cycles; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d	V(SC)d
Analysis set: safety	39	40
Distribution of subjects treated in and beyond each cycle, n (%)		
≥ 1 cycle	39 (100.0%)	40 (100.0%)
≥ 2 cycles	38 (97.4%)	36 (90.0%)
≥ 3 cycles	35 (89.7%)	33 (82.5%)
≥ 4 cycles	32 (82.1%)	32 (80.0%)
≥ 5 cycles	25 (64.1%)	25 (62.5%)
≥ 6 cycles	14 (35.9%)	21 (52.5%)
≥ 7 cycles	13 (33.3%)	19 (47.5%)
≥ 8 cycles	10 (25.6%)	17 (42.5%)
≥ 9 cycles	0	0
Total number of treatment cycles received, n (%)		
1	1 (2.6%)	4 (10.0%)
2	3 (7.7%)	3 (7.5%)
3	3 (7.7%)	1 (2.5%)
4	7 (17.9%)	7 (17.5%)

Table 3: Summary of Treatment Cycles; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d	V(SC)d
5	11 (28.2%)	4 (10.0%)
6	1 (2.6%)	2 (5.0%)
7	3 (7.7%)	2 (5.0%)
8	10 (25.6%)	17 (42.5%)
9+	0	0
Summary of total number of treatment cycles received		
N	39	40
Mean (SD)	5.3 (2.06)	5.6 (2.54)
Median	5.0	6.0
Range	(1; 8)	(1; 8)

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone.
Note: Percentages are calculated with the number of subjects in each treatment group as denominator.
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As was reported in the primary CSR, the overall median dose intensity (mg/m^2/cycle) for both VELCADE and dexamethasone were similar between the two treatment groups (Table 4). The median duration of treatment was 15.71 weeks in V(IV)d group and 19.21 weeks in V(SC)d group. The overall median dose intensity (mg/m^2/cycle) was 4.73 in V(IV)d group and 4.75 in V(SC)d group.

Table 4: Summary of Duration of Study Treatment and Dose Intensity; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d	V(SC)d
Analysis set: safety	39	40
Duration of study treatment (weeks)		
N	39	40
Mean (SD)	17.27 (8.579)	17.57 (9.828)
Median	15.71	19.21
Range	(1.7; 37.4)	(1.3; 49.1)
VELCADE dose intensity (mg/m^2/cycle)[a]		
N	39	40
Mean (SD)	4.64 (0.554)	4.70 (0.541)
Median	4.73	4.75
Range	(3.3; 5.3)	(3.1; 5.5)
VELCADE dose intensity (Cycles 1-4, mg/m^2/cycle)[a]		
N	39	40
Mean (SD)	4.88 (0.452)	4.80 (0.510)
Median	5.08	4.98
Range	(3.8; 5.3)	(3.1; 5.4)
VELCADE dose intensity (Cycles 5+, mg/m^2/cycle)[a]		
N	25	25
Mean (SD)	3.79 (1.324)	4.52 (0.801)
Median	4.01	4.94
Range	(1.0; 5.3)	(2.5; 5.5)
Dexamethasone dose intensity (mg/cycle)[b]		
N	39	40
Mean (SD)	142.94 (29.677)	139.48 (27.239)
Median	157.95	153.39
Range	(54.0; 162.0)	(72.0; 162.0)
Dexamethasone dose intensity (Cycles 1-4, mg/cycle)[b]		
N	39	40
Mean (SD)	147.56 (26.686)	145.65 (23.990)
Median	162.00	162.00
Range	(58.5; 162.0)	(78.0; 162.0)

Table 4: Summary of Duration of Study Treatment and Dose Intensity; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d	V(SC)d
Dexamethasone dose intensity (Cycles 5+, mg/cycle)[b]		
N	25	25
Mean (SD)	122.64 (51.777)	130.37 (43.248)
Median	162.00	162.00
Range	(20.6; 162.0)	(48.0; 162.0)

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone.
[a] Dose intensity (mg/m^2/cycle) is calculated as the sum of total doses (mg/m^2) received in all cycles divided by the number of treatment cycles on VELCADE.
[b] Dose intensity (mg/cycle) is calculated as the sum of total doses (mg) received in all cycles divided by the number of treatment cycles on dexamethasone.
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Cycle Delays and Treatment Modifications

Attachment TSIEXP05 summarizes the incidence of and reasons for cycle delays and dose modifications (dose skip, and dose reduce) for both VELCADE and dexamethasone. Although the 2 subjects in V(SC)d group were ongoing treatment at the original data cutoff, no additional cycle delay and dose modification were reported during the long-term extension. As was reported in the primary CSR, cycle delays were reported for 56.4% of subjects in the V(IV)d group and 55% of subjects in the V(SC)d group. The most common reason for delay was AEs (51.3% and 42.5% of subjects, respectively). Similar percent of skipped doses of VELCADE were reported in the V(IV)d group (38.5% of subjects) and V(SC)d group (37.5% of subjects), with the most common reason being AEs. A higher percent of subjects (51.3%) in V(IV)d group were administered reduced doses for VELCADE due to AEs as compared to V(SC)d group (32.5%).

PHARMACOKINETIC RESULTS:

No new pharmacokinetic analyses were conducted for the long-term extension of Study MMY3037.

EFFICACY RESULTS:

Overall, 81 subjects (40 in V[IV]d and 41 in V[SC]d) were included in the ITT set; 76 subjects (38 subjects each in V[IV]d group and V[SC]d group) were included in the response-evaluable set.

Primary Efficacy Analysis:

The primary CSR incorporates complete information for the primary endpoint of ORR after 4 cycles. The results are presented in Section 6.2 of the primary CSR.

The ORR were 70.0% for V(IV)d and 65.9% for V(SC)d based on ITT population. The stratified Mantel Haenszel-estimate of the relative risk of achieving response for SC vs. IV was 0.93 with 95% CI (0.69, 1.27).

All the sensitivity results on the ORR after 4 Cycles were similar to those in the ITT population.

Major Secondary Analyses:

CR, VGPR rates (VGPR or better rate) after 4 Cycles of Vd treatment

The primary CSR incorporates complete information for the analysis of VGPR or better rate after 4 cycles. The results are presented in Section 6.3.1 of the primary CSR.

Based on ITT population, V(IV)d group and V(SC)d group had similar percentage of subjects achieving VGPR or better after 4 Cycles (32.5% in V[IV]d vs. 34.1% in V[SC]d), with rate difference of SC-IV: 1.6% [95% CI: -18.9%, 22.2%].

The sensitivity analyses results were similar to that observed in the ITT analysis set.

ORR (CR+ VGPR+ PR) after 8 Cycles of Vd treatment

Table 5 summarizes overall best response in the ITT population after 8 cycles of treatment. The ORRs (70.0% in V[IV]d group and 65.9% in V[SC]d group) are unchanged from the MMY3037 primary CSR. In the V(IV)d treatment group, CR rate and VGPR rate after 8 Cycles for the final analysis was little changed from the primary analysis as reported in primary CSR. One subject reported as achieving VGPR in the primary analysis was reported as achieving CR in the final analysis (primary/final VGPR: 6 [15.0%] subjects/5 [12.5%] subjects; primary/final CR: 9 [22.5%] subjects/10 [25.0%] subjects). This triggered changes in the VGPR rate and CR rate difference of SC-IV (primary VGPR 9.4% [-7.8%, 26.6%], final VGPR 11.9% [-4.8%, 28.6%]; primary CR -5.4% [-22.8%, 11.9%], final CR -7.9% [-25.6%, 9.8%]). No other changes in overall response after 8 Cycles were noted. As noted in primary CSR, more subjects (7 [17.1%] in V[SC]d group and 10 [25.0%] in V[IV]d group) had best response CR after 8 Cycles compared with those after 4 Cycles (5 [12.2%] subjects in V[SC]d group and 2 [5.0%] subjects in V[IV]d group).

The sensitivity analyses results based on response-evaluable population were similar to that observed in the ITT analysis set (Attachment TEFRESP03A). Overall best response after 8 cycles of treatment based on investigator assessment for ITT set, and response-evaluable subjects, are presented in Attachment TEFRESP04, and Attachment TEFRESP04A, respectively. The results were robust and consistent across multiple sensitivity analyses.

Table 5: Summary of Best Confirmed Response during First 8 Cycles Based on Computerized Algorithm; Intent-to-treat Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)	V(SC)d n (%)	Rate Difference [a] (95% CI)	Relative Risk [b] (95% CI)
Analysis set: intent-to-treat	40	41		
Response category				
Complete response (CR)	10 (25.0%)	7 (17.1%)	-7.9% (-25.6%, 9.8%)	
Very good partial response (VGPR)	5 (12.5%)	10 (24.4%)	11.9% (-4.8%, 28.6%)	
Partial response (PR)	13 (32.5%)	10 (24.4%)	-8.1% (-27.7%, 11.5%)	
Minimal Response (MR)	3 (7.5%)	3 (7.3%)	-0.2% (-11.6%, 11.2%)	
Stable disease (SD)	6 (15.0%)	6 (14.6%)		
Progressive disease (PD)	1 (2.5%)	2 (4.9%)		
Not evaluable (NE)	2 (5.0%)	3 (7.3%)		
Overall response (CR+VGPR+PR)	28 (70.0%)	27 (65.9%)	-4.1% (-24.5%, 16.2%)	0.93 (0.69, 1.27)
VGPR or better (CR + VGPR)	15 (37.5%)	17 (41.5%)	4% (-17.3%, 25.2%)	

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone. CI = confidence interval.
Note: Response was assessed by computerized algorithm, based on International Uniform Response Criteria Consensus Recommendations. Percentages are calculated with the number of subjects in each group as denominator.
[a] 95% CI for SC rate - IV rate is based on normal approximation.
[b] Stratified Mantel-Haenszel estimate of the common relative risk of V(SC)d vs. V(IV)d is used. The stratification factors are: ISS staging (I, II, III) and number of prior lines of therapy (1 vs. >1).
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Progression-Free Survival

PFS for the long-term extension was estimated for the ITT population (Table 6). In both treatment groups, 4 censored subjects in the primary analysis were reclassified as with PFS events in the final analysis. As compared with the primary analysis presented in the MMY3037 CSR, increases in the numbers of subjects with events, and decreases in the numbers of subjects censored, reflect 6 months of additional follow-up for the long-term extension. With a cutoff date of 10 November 2018, the median PFS was 9.26 months (95% CI: 7.39 to 14.06) and 7.49 months (95% CI: 4.96 to 9.23) for V(IV)d and V(SC)d, respectively, with 21 (52.5%) and 25 (61.0%) subjects with PFS events in each group. The hazard ratio (SC versus IV) was 1.34 (95% CI: 0.72, 2.47).

With a cutoff date of 07 May 2018, the MMY3037 primary CSR reported a median PFS of 9.23 months (95% CI: 7.39, NE) and 7.49 months (95% CI: 4.96, 9.23) for V(IV)d and V(SC)d, respectively, with 17 (42.5%) and 21 (51.2%) PFS events in each group, and a hazard ratio of 1.55 (95% CI: 0.81, 2.97).

PFS findings for the long-term extension were consistent with those reported in the MMY3037 primary CSR, and with a smaller hazard ratio of SC versus IV which indicates that the hazard rate of PFS event in V(SC)d group become closer to V(IV)d group in the long-term extension period.

Although no significant difference between the PFS of V(IV)d and V(SC)d groups was indicated by the hazard ratio and its 95% CI, the numerical difference in median PFS were still observed between the two treatment groups. It was likely to be due to the data variation introduced by small sample size. The 6-month PFS rate was 69.2% for V(IV)d group vs. 57.7% for V(SC)d group. The 12-month PFS rate was 47.5% for V(IV)d group vs. 27.5% for V(SC)d group. A Kaplan-Meier plot for PFS is provided as in Figure 1.

The sensitivity analyses results based on investigator assessment, for the response-evaluable analysis set based on computerized algorithm, and for the response-evaluable population, based on investigator assessment, are presented in Attachment TEFPFS02, Attachment TEFPFS01A and, Attachment TEFPFS02A, respectively. The results were consistent across multiple sensitivity analyses and as those based on computerized algorithm for the ITT population. Kaplan-Meier plot for PFS based on computer algorithm (response-evaluable analysis set), and on investigator assessment (intent-to-treat analysis set and response-evaluable analysis set) are presented as Attachment GEFPFS01A, Attachment GEFPFS02, and Attachment GEFPFS02A, respectively.

Table 6: Summary of Progression-free Survival Based on Computerized Algorithm; Intent-to-treat Analysis Set (Study 26866138MMY3037)

	V(IV)d	V(SC)d
Analysis set: intent-to-treat	40	41
Progression-free survival (PFS)		
Number of events (%)	21 (52.5%)	25 (61.0%)
Number of censored (%)	19 (47.5%)	16 (39.0%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	4.86 (2.07, 8.25)	4.17 (1.41, 5.95)
Median (95% CI)	9.26 (7.39, 14.06)	7.49 (4.96, 9.23)
75% quantile (95% CI)	14.95 (12.91, NE)	14.78 (8.31, 20.17)
Hazard ratio (95% CI)[a]		1.34 (0.72, 2.47)
6-month PFS rate % (95% CI)	69.2 (51.2, 81.7)	57.7 (39.0, 72.6)
12-month PFS rate % (95% CI)	47.5 (28.0, 64.8)	27.5 (12.6, 44.6)

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone. CI = confidence interval.
[a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, vs. III), and number of prior lines of therapy (1 vs. >1). A hazard ratio <1 indicates an advantage for V(SC)d.
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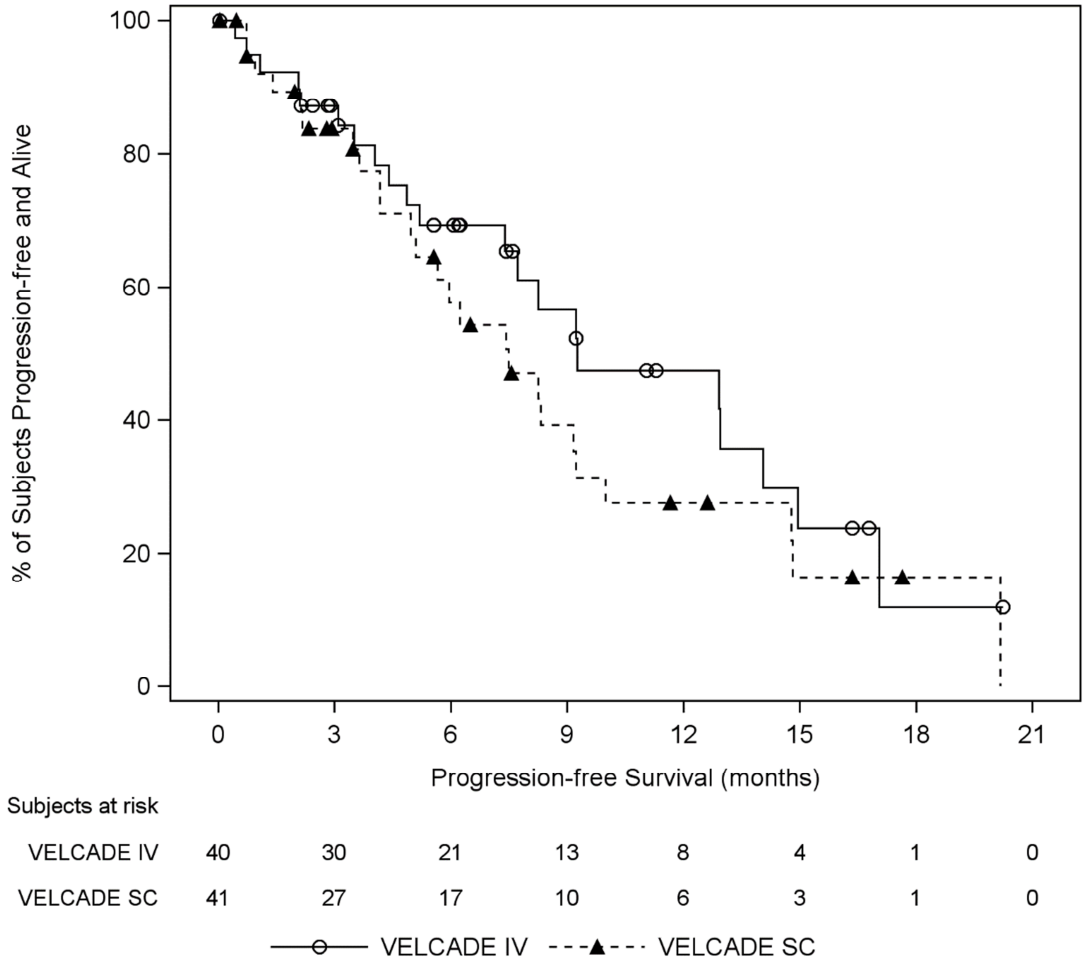
Figure 1: Kaplan-Meier Plot for Progression-free survival Based on Computer Algorithm; Intent-to-treat Analysis Set (Study 26866138MMY3037)



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1-year survival rate

1-year survival rate for the long-term extension was estimated for the ITT population and is presented in Table 7. The difference in 1-year survival rate between the V(SC)d and V(IV) arms noted in the primary analysis became smaller in the final analysis. The updated 1-year survival rate was 75.2% for the V(SC)d treatment group, compared with 89.3% for the V(IV)d treatment group, a difference of 14.1%. The primary CSR reported 1-year survival rates of 75.2% and 92.2% for the V(SC)d and V(IV)d treatment groups, respectively, a difference of 17.0%. After a median follow-up of 15.97 months (Table 2), the death events were 5 (12.5%) in V(IV)d group and 10 (24.4%) in V(SC)d group. The median OS was not reached for either treatment group due to small number of death events. A Kaplan-Meier plot for OS is provided in Figure 2. The median OS estimates were not considered reliable, as the Kaplan-Meier curves did not either cross or was even close to the median line at the maximum follow-up.

Table 7: Summary of Overall Survival; Intent-to-treat Analysis Set (Study 26866138MMY3037)

	V(IV)d	V(SC)d
Analysis set: intent-to-treat	40	41
Overall survival		
Number of events (%)	5 (12.5%)	10 (24.4%)
Number of censored (%)	35 (87.5%)	31 (75.6%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	NE (7.00, NE)	17.35 (5.55, NE)
Median (95% CI)	NE (NE, NE)	NE (17.35, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI)[a]		2.11 (0.72, 6.18)
12-month survival rate % (95% CI)	89.3 (73.8, 95.8)	75.2 (56.2, 86.8)

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone. CI = confidence interval.
[a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable. A hazard ratio <1 indicates an advantage for V(SC)d.

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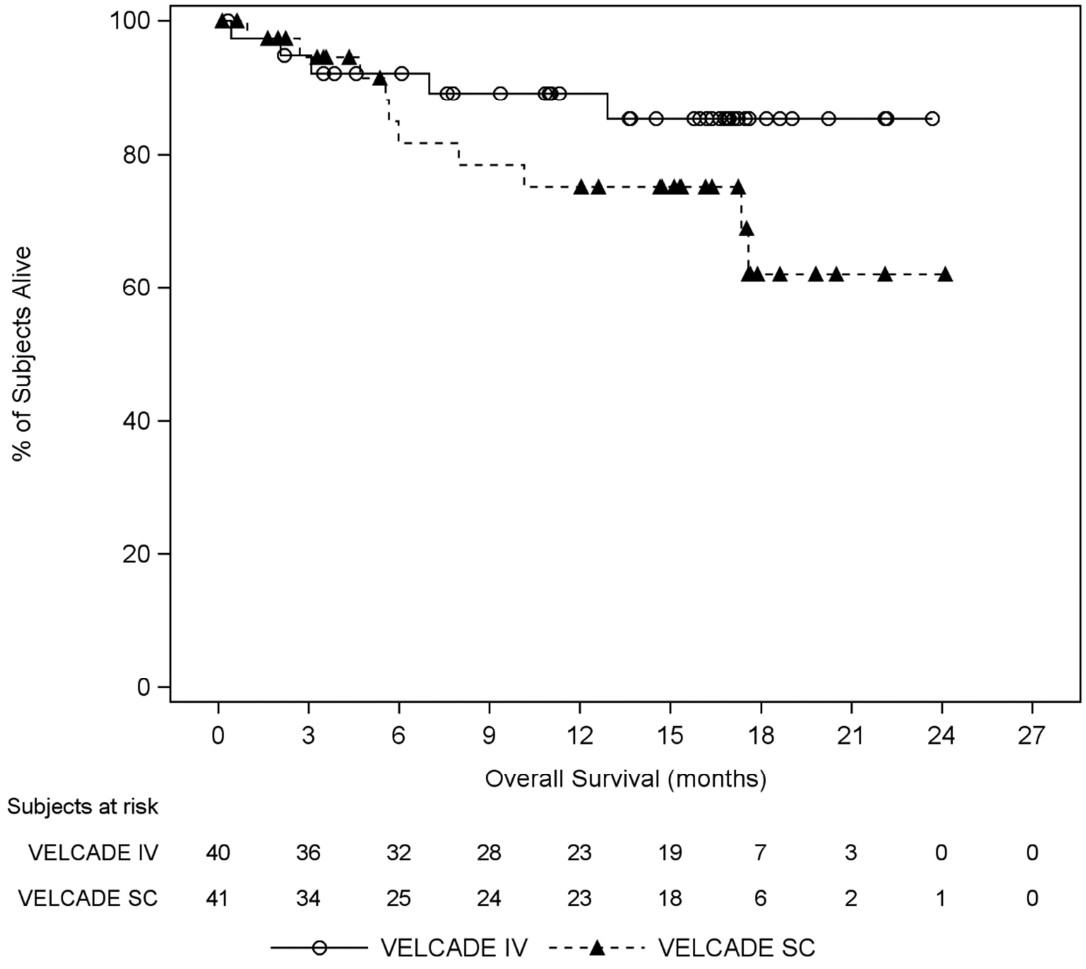
Figure 2: Kaplan-Meier Plot for Overall Survival; Intent-to-treat Analysis Set (Study 26866138MMY3037)



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Thirty-five (87.5%) subjects in the V(IV)d group and 31 (75.6%) subjects in the V(SC)d group were censored for overall survival. The main reasons for censoring of OS based on ITT Set were completed the study (17 [48.6%] subjects in V(IV)d group and 18 [58.1%] subjects in V(SC)d group) followed by withdrawal of consent to study participation (9 [25.7%] subjects in V(IV)d group and 11 [35.5%] subjects in V(SC)d group), physician decision (7 [20.0%] subjects in V(IV)d group and 1 [3.2%] subjects in V(SC)d group), and other (2 [5.7%] subjects in V(IV)d group and 1 [3.2%] subject in V(SC)d group) (Attachment TEFRFOS01).

Time to response/Time to best response

Time to first response and time to best response for the long-term extension were analyzed for responders in the ITT population (Table 8). As one subject in V(IV)d group reported as achieving VGPR in the primary analysis was reported as achieving CR in the final analysis for long-term extension, summary results for time to best response in V(IV)d group were slightly different from those in primary CSR. The median time to first response was similar (0.72 months) in V(IV)d group and V(SC)d group, and the median time to best response for responders (1.43 months in V[IV]d group vs. 2.10 months in V[SC]d group) were unchanged from those reported in the primary CSR.

Table 8: Descriptive Summary of Time to Response; Responders in the Intent-to-treat Analysis Set (Study 26866138MMY3037)

	V(IV)d	V(SC)d
Analysis set: responders in the intent-to-treat	28	27
Time to first response[a] (months)		
N	28	27
Mean (SD)	0.97 (0.401)	1.06 (0.560)
Median	0.72	0.72
Range	(0.7; 2.3)	(0.7; 2.6)
Time to best response[a] (months)		
N	28	27
Mean (SD)	2.43 (2.034)	2.46 (1.636)
Median	1.43	2.10
Range	(0.7; 7.9)	(0.7; 7.0)

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone
[a] Response PR or better.
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Time to progression

TTP for the long-term extension was calculated for the ITT population based on the computerized algorithm (Table 9). In both treatment groups, 4 censored subjects in the primary analysis were reclassified as with time to disease progression events in the final analysis. As compared with the primary analysis presented in the MMY3037 CSR, increases in the numbers of subjects with events, and decreases in the numbers of subjects censored, reflect 6 months of additional follow-up for the long-term extension. With a cutoff date of 10 November 2018, the median TTP was 12.91 months (95% CI: 7.72 to 14.95) and 8.25 months (95% CI: 5.09 to 9.99) for V(IV)d and V(SC)d, respectively, with 18 (45.0%) and 23 (56.1%) TTP events. The hazard ratio (SC versus IV) was 1.49 (95% CI: 0.77, 2.87).

With a cutoff date of 07 May 2018, the MMY3037 primary CSR reported a median TTP of 9.26 months (95% CI: 7.72 to NE) and 8.25 months (95% CI: 5.09 to 9.99) for V(IV)d and V(SC)d, respectively, with 14 (35.0%) and 19 (46.3%) TTP events, and a hazard ratio of 1.76 (0.87, 3.58). TTP findings for the long-term extension were consistent with those reported in the MMY3037 primary CSR, and with a smaller hazard ratio of SC versus IV which indicates that the hazard rate of TTP event in V(SC)d group become closer to V(IV)d group in the long-term extension period.

Although no significant difference between the TTP of V(IV)d and V(SC)d groups was indicated by the hazard ratio and its 95% CI, the numerical difference in median PFS were still observed between the two treatment groups. It was likely to be due to the data variation introduced by small sample size. A Kaplan-Meier plot for TTP (computer algorithm; ITT) is provided in Figure 3.

Median TTP for the response-evaluable analysis set based on computerized algorithm was similar to that presented in the ITT set (Attachment TEFTTP01A). As a sensitivity analysis, TTP was also evaluated based on investigators assessment. Summary of TTP for ITT population and response-evaluable population were provided in Attachment TEFTTP02 and Attachment TEFTTP02A, respectively. These results were similar as those based on primary method. A Kaplan-Meier plot for TTP (investigator assessment; ITT) provided in Attachment GEFTTP02.

Table 9: Summary of Time to Disease Progression Based on Computerized Algorithm; Intent-to-treat Analysis Set (Study 26866138MMY3037)

	V(IV)d	V(SC)d
Analysis set: intent-to-treat	40	41
Time to disease progression		
Number of events (%)	18 (45.0%)	23 (56.1%)
Number of censored (%)	22 (55.0%)	18 (43.9%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	7.39 (3.52, 9.23)	4.17 (2.14, 6.24)
Median (95% CI)	12.91 (7.72, 14.95)	8.25 (5.09, 9.99)
75% quantile (95% CI)	17.05 (12.91, NE)	14.78 (8.31, 20.17)
Hazard ratio (95% CI)[a]		1.49 (0.77, 2.87)

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone. CI = confidence interval.
[a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, vs. III), and number of prior lines of therapy (1 vs. >1). A hazard ratio <1 indicates an advantage for V(SC)d.
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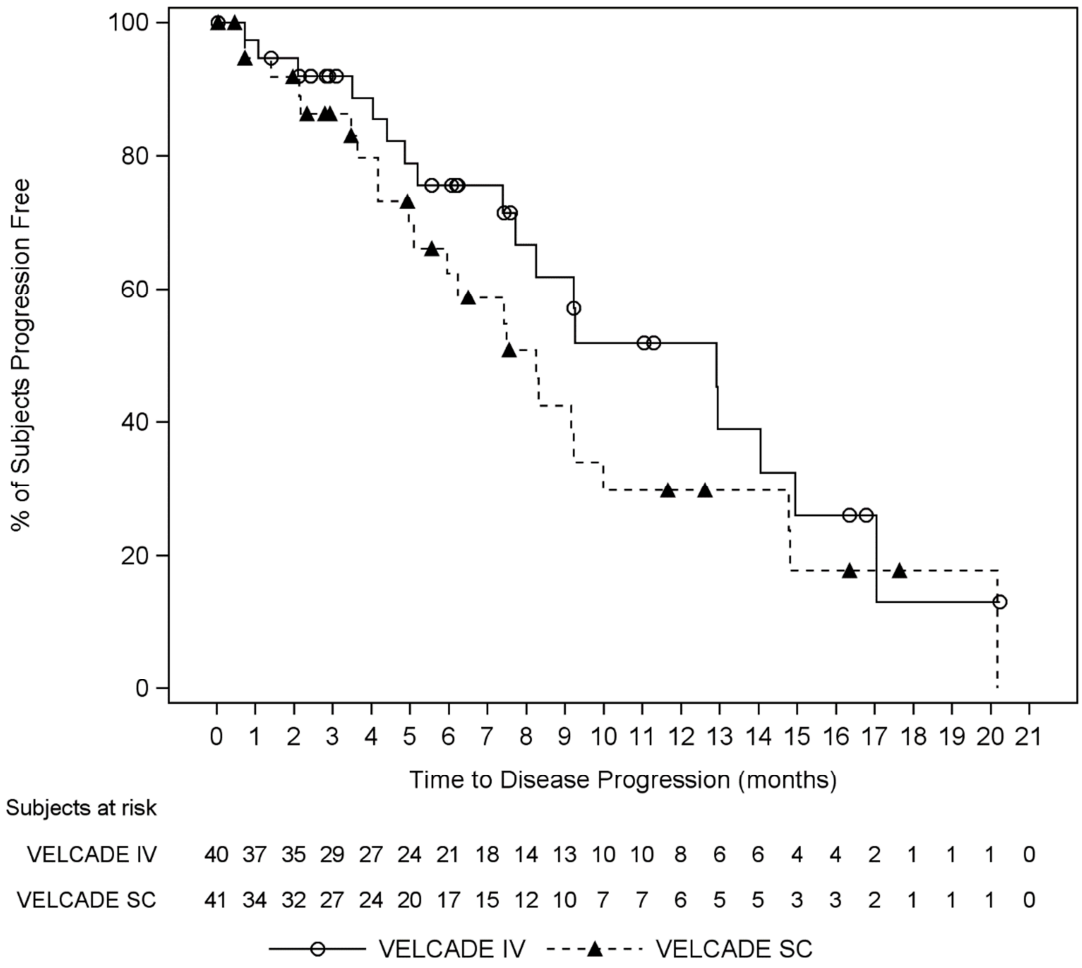
Figure 3: Kaplan-Meier Plot for Time to Disease Progression Based on Computer Algorithm; Intent-to-treat Analysis Set (Study 26866138MMY3037)



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Duration of response

A summary of duration of response for long-term extension based on computerized algorithm is presented in Table 10. In both treatment groups, 4 censored subjects in the primary analysis were reclassified as with DOR events in the final analysis. The median DOR for responders in V(IV)d group was 12.22 months (95% CI: 8.51 to 16.36) and 7.82 months (95% CI: 6.67 to 14.13) for V(SC)d group, which are similar to results in primary CSR. The 6-month event-free rate in V(IV)d group was 86.4% (95% CI: 63.4, 95.4) and 73.7% (95% CI: 50.5, 87.2) for V(SC)d group. The 12-month event-free rate in V(IV)d group was 56.9% (95% CI: 28.2, 77.8) and 37.2% (95% CI: 17.1, 57.5) for V(SC)d group. A Kaplan-Meier plot for DOR is presented in Figure 4.

Table 10: Summary of Duration of Response Based on Computerized Algorithm; Responders in the Intent-to-treat Analysis Set (Study 26866138MMY3037)

	V(IV)d	V(SC)d
Analysis set: responders (PR or better) in the intent-to-treat analysis set	28	27
Duration of response[a]		
Number of events (%)	11 (39.3%)	16 (59.3%)
Number of censored (%)	17 (60.7%)	11 (40.7%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	8.51 (2.69, 12.22)	4.17 (2.43, 7.62)
Median (95% CI)	12.22 (8.51, 16.36)	7.82 (6.67, 14.13)
75% quantile (95% CI)	16.36 (12.22, 16.36)	14.13 (7.92, 18.79)
6-month event-free[b] rate % (95% CI)	86.4 (63.4, 95.4)	73.7 (50.5, 87.2)
12-month event-free[b] rate % (95% CI)	56.9 (28.2, 77.8)	37.2 (17.1, 57.5)

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone. CI = confidence interval; PR = Partial response.
[a] First response PR or better.
[b] Event-free days is calculated from the date of first confirmed response.
Note: Number of events refers to number of responders (PR or better) who developed disease progression or died due to disease progression.
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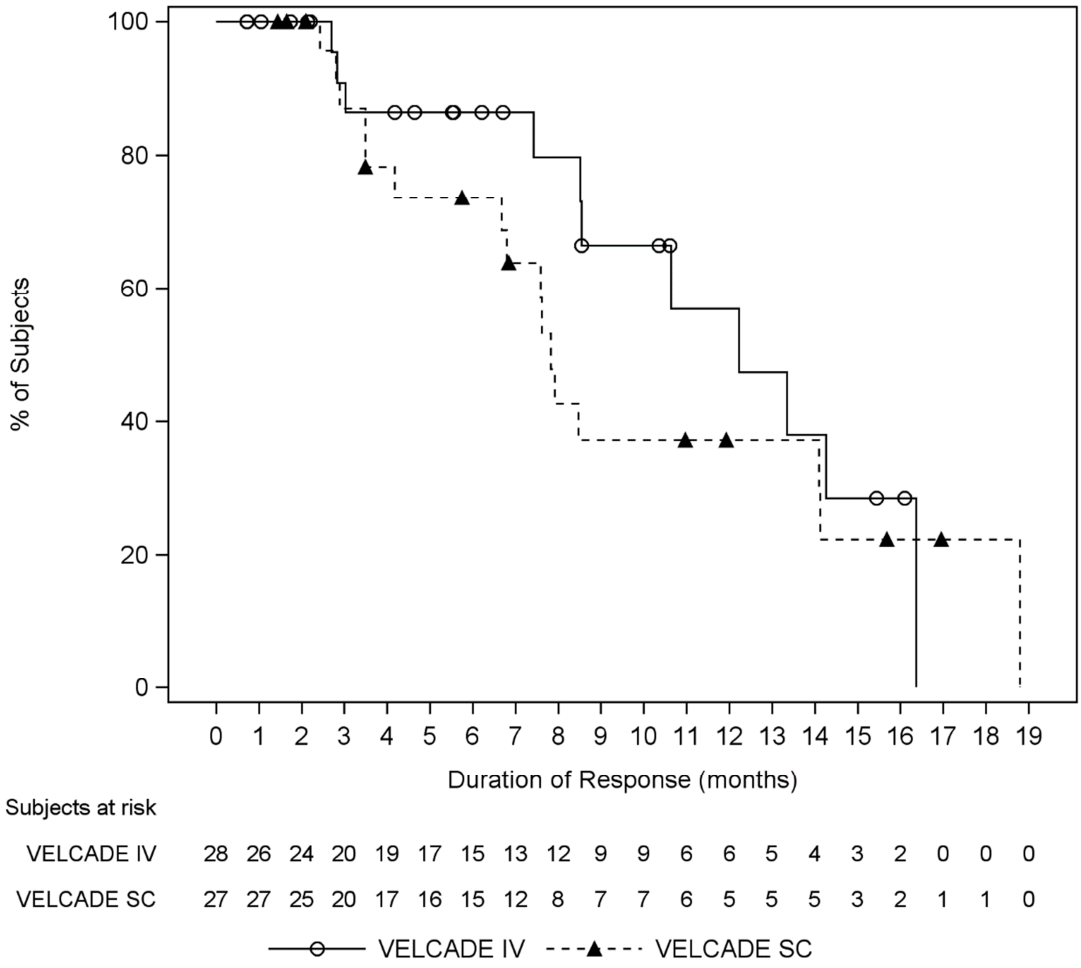
Figure 4: Kaplan-Meier Plot for Duration of Response; Responders in the Intent-to-treat Analysis Set (Study 26866138MMY3037)



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Other Secondary Analyses:

Best M-protein/dFLC Response

Best M-protein/dFLC response after 4 cycles based on response-evaluable population is presented in Section 6.4.1 of the primary CSR. Although one subject in V(IV)d group reported as achieving VGPR in the primary analysis was reported as achieving CR in the final analysis for long-term extension, the results of best M-protein/dFLC response after 8 cycles (Attachment TEFMRSP02) were unchanged from those reported in primary CSR.

Time to Subsequent Antimyeloma Therapy

Alternative multiple myeloma therapy following discontinuation of study treatment was initiated in 3 more subjects in V(IV)d and 2 more subjects in V(SC)d (primary/final in V[IV]d: 10 [25.0%] subjects/13 [32.5%] subjects; primary/final in V[SC]d: 15 [36.6%] subjects/17 [41.5%] subjects) in the final analysis (Attachment TEFTTSAT01). Median time to subsequent antimyeloma therapy was NE (95% CI: 9.26, NE) in V(IV)d and 11.50 months (95% CI: 6.44, NE) in V(SC)d. The Kaplan-Meier plot of time to subsequent antimyeloma therapy for V(IV)d and V(SC)d is provided in Attachment GEFTTSAT01.

Subgroup Analysis of Efficacy Endpoints:

Subgroup analysis is presented in Section 6.5 of the primary CSR, no new analyses were conducted for the final analysis.

Efficacy Summary:

At the time of the primary data cutoff for Study MMY3037 (07 May 2018), 28 subjects in the V(IV)d treatment group and 24 subjects in the V(SC)d treatment group were still in the study, and 2 of the 24 subjects in the V(SC)d treatment group and no subjects from the V(IV)d treatment group were still on treatment. With very few additional data collected during the treatment phase, the final analyses (10 November 2018 cutoff) produced no changes to response rates for the first 4 cycles, and only minor changes for the V(SC)d treatment group for the first 8 cycles. For all categories of response evaluated, response rates remained consistent between the V(SC)d and V(IV)d treatment groups.

With 6 months of additional follow-up data available for the long-term extension (median duration of follow-up of 15.97 months versus the primary analyses of 8.97 months), updated results were generated for the time-to-event endpoints of TTP, PFS, 1-year survival, time to response/best response, and duration of response. The additional events captured after the 07 May 2018 cutoff did not change the overall efficacy conclusion as reported in the primary CSR, that VELCADE SC demonstrated comparable efficacy as compared to VELCADE IV when combined with dexamethasone, as supported by the predefined analyses of primary and secondary endpoints.

The difference in 1-year survival rate between the V(SC)d and V(IV) arms, and hazard ratio of PFS and TTP for V(SC)d versus V(IV)d noted in the primary analysis became smaller in the final analysis. Still, the 1-year OS rate was numerically higher in V(IV)d (89.3%) group as compared to V(SC)d (75.2%) group. The median OS was not reached for either treatment group due to small number of death events.

SAFETY RESULTS:

Updated narratives for the following event categories will be attached at the end of this report: deaths within 30 days of last dose, subjects with drug-related SAEs, subjects who discontinued due to AEs assessed as related to study drug(s), subjects who had ≥Grade 3 adverse events(s) of special interest (herpes zoster, heart failure, ventricular rhythm abnormalities, and peripheral neuropathy).

Safety results are based on 79 subjects (39 subjects in V[IV]d and 40 subjects in V[SC]d) who were randomized and received at least 1 dose of study drug (safety population).

Adverse Events:

Summary of All Adverse Events

An overview of the TEAEs by treatment group is presented in Table 11. This table is unchanged from that presented in the primary CSR. There is no important difference between the treatment groups.

Table 11: Overview of Treatment-emergent Adverse Events; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)	V(SC)d n (%)
Analysis set: safety	39	40
Any TEAE	39 (100.0%)	40 (100.0%)
At least one related[a]	37 (94.9%)	39 (97.5%)
At least one related to VELCADE	37 (94.9%)	37 (92.5%)
At least one related to dexamethasone	35 (89.7%)	36 (90.0%)
Maximum toxicity grade		
Grade 1	0	0
Grade 2	6 (15.4%)	7 (17.5%)

Table 11: Overview of Treatment-emergent Adverse Events; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)	V(SC)d n (%)
Grade 3	22 (56.4%)	27 (67.5%)
Grade 4	8 (20.5%)	4 (10.0%)
Grade 5	3 (7.7%)	2 (5.0%)
Any serious TEAE	24 (61.5%)	22 (55.0%)
At least one related[a]	21 (53.8%)	20 (50.0%)
At least one related to VELCADE	17 (43.6%)	17 (42.5%)
At least one related to dexamethasone	17 (43.6%)	18 (45.0%)
TEAE leading to discontinuation of study treatment[b]	12 (30.8%)	10 (25.0%)
TEAE leading to discontinuation of VELCADE	12 (30.8%)	10 (25.0%)
At least one related to VELCADE	10 (25.6%)	8 (20.0%)
TEAE leading to discontinuation of dexamethasone	13 (33.3%)	10 (25.0%)
At least one related to dexamethasone	4 (10.3%)	6 (15.0%)
TEAE with outcome of death	3 (7.7%)	2 (5.0%)
At least one related to VELCADE	0	2 (5.0%)
At least one related to dexamethasone	0	2 (5.0%)

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone.
TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 2 study treatment: VELCADE and dexamethasone.
[b] Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
Note: Adverse events are reported using MedDRA version 20.0. Percentages are calculated with the number of subjects in each group as denominator.
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Table 12 presents the incidence of ≥10% TEAEs by MedDRA SOC and preferred term (PT) for the safety population, as of the long-term extension data cutoff date. As was reported in the primary CSR, the most frequently reported TEAEs in both the groups were thrombocytopenia, peripheral sensory neuropathy, anemia, diarrhea, cough, upper respiratory tract infection, lung infection, neutropenia, leukopenia, and hypokalemia. For these TEAEs, rates were unchanged versus those presented in the primary CSR, with the exceptions of anaemia, leukopenia, and hypokalaemia, anaemia and leukopenia each showed an additional subject for V(IV)d treatment group, while leukopenia and hypokalaemia each showed an additional subject for V(SC)d treatment group.

There appeared to be a trend towards lower incidence of SOC of nervous system disorders for V(SC)d group (76.9% in V[IV]d vs. 57.5% in V[SC]d) due to differences in peripheral sensory neuropathy (53.8% in V[IV]d vs. 22.5% in V[SC]d). For general disorders and administration site condition SOC (51.3% vs. 70.0%), there appeared to be a trend towards higher incidence for V(SC)d. Adverse events with a >15% difference between the 2 treatment groups are: thrombocytopenia (32 [82.1%] vs. 26 [65%]), and erythema (1 [2.6%] vs. 7 [17.5%], respectively).

Table 12: Most Common (at Least 10%) Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)	V(SC)d n (%)
Analysis set: safety	39	40
Total number of subjects with TEAE	39 (100.0%)	40 (100.0%)
MedDRA system organ class/Preferred term		
Blood and lymphatic system disorders	35 (89.7%)	34 (85.0%)
Thrombocytopenia	32 (82.1%)	26 (65.0%)
Anaemia	17 (43.6%)	18 (45.0%)
Leukopenia	9 (23.1%)	13 (32.5%)

Table 12: Most Common (at Least 10%) Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)	V(SC)d n (%)
Neutropenia	12 (30.8%)	10 (25.0%)
Lymphopenia	9 (23.1%)	8 (20.0%)
Leukocytosis	6 (15.4%)	5 (12.5%)
Eosinopenia	4 (10.3%)	2 (5.0%)
Infections and infestations	33 (84.6%)	33 (82.5%)
Upper respiratory tract infection	13 (33.3%)	16 (40.0%)
Lung infection	13 (33.3%)	9 (22.5%)
Pneumonia	6 (15.4%)	6 (15.0%)
Conjunctivitis	2 (5.1%)	4 (10.0%)
Bronchitis	4 (10.3%)	2 (5.0%)
Herpes zoster	6 (15.4%)	2 (5.0%)
Metabolism and nutrition disorders	24 (61.5%)	29 (72.5%)
Hypokalaemia	9 (23.1%)	13 (32.5%)
Hyperglycaemia	10 (25.6%)	10 (25.0%)
Hyperuricaemia	5 (12.8%)	9 (22.5%)
Hypoalbuminaemia	5 (12.8%)	6 (15.0%)
Hypoproteinaemia	4 (10.3%)	5 (12.5%)
Hypercholesterolaemia	2 (5.1%)	4 (10.0%)
Hypertriglyceridaemia	1 (2.6%)	4 (10.0%)
Hypocalcaemia	4 (10.3%)	3 (7.5%)
Hyponatraemia	4 (10.3%)	2 (5.0%)
General disorders and administration site conditions	20 (51.3%)	28 (70.0%)
Oedema peripheral	3 (7.7%)	9 (22.5%)
Pyrexia	10 (25.6%)	8 (20.0%)
Fatigue	2 (5.1%)	6 (15.0%)
Asthenia	3 (7.7%)	5 (12.5%)
Injection site erythema	0	4 (10.0%)
Gastrointestinal disorders	27 (69.2%)	25 (62.5%)
Diarrhoea	15 (38.5%)	13 (32.5%)
Abdominal distension	8 (20.5%)	6 (15.0%)
Constipation	10 (25.6%)	6 (15.0%)
Abdominal pain upper	1 (2.6%)	4 (10.0%)
Nausea	4 (10.3%)	2 (5.0%)
Vomiting	4 (10.3%)	1 (2.5%)
Investigations	28 (71.8%)	25 (62.5%)
Alanine aminotransferase increased	6 (15.4%)	7 (17.5%)
Neutrophil count increased	6 (15.4%)	7 (17.5%)
Aspartate aminotransferase increased	4 (10.3%)	6 (15.0%)
Weight decreased	10 (25.6%)	6 (15.0%)
Gamma-glutamyltransferase increased	2 (5.1%)	5 (12.5%)
Blood alkaline phosphatase increased	6 (15.4%)	4 (10.0%)
Albumin globulin ratio increased	4 (10.3%)	0
Nervous system disorders	30 (76.9%)	23 (57.5%)
Peripheral sensory neuropathy	21 (53.8%)	9 (22.5%)
Dizziness	0	4 (10.0%)
Neurotoxicity	4 (10.3%)	3 (7.5%)
Respiratory, thoracic and mediastinal disorders	18 (46.2%)	18 (45.0%)
Cough	14 (35.9%)	9 (22.5%)
Productive cough	5 (12.8%)	3 (7.5%)
Skin and subcutaneous tissue disorders	9 (23.1%)	11 (27.5%)
Erythema	1 (2.6%)	7 (17.5%)
Psychiatric disorders	10 (25.6%)	9 (22.5%)
Insomnia	10 (25.6%)	7 (17.5%)
Renal and urinary disorders	5 (12.8%)	6 (15.0%)

Table 12: Most Common (at Least 10%) Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)	V(SC)d n (%)
Renal impairment	4 (10.3%)	1 (2.5%)
Hepatobiliary disorders	5 (12.8%)	4 (10.0%)
Hyperbilirubinaemia	5 (12.8%)	3 (7.5%)

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone.
TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA version 20.0. Percentages are calculated with the number of subjects in each group as denominator.
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Most common (at least 5%) grade 3 or 4 treatment-emergent adverse events by MedDRA system organ class and preferred term is presented in Table 13. This table is unchanged from that presented in the primary CSR. The incidence of Grade 3 or 4 TEAEs was similar for the V(IV)d group (33 [84.6%]) and the V(SC)d group (33 [82.5%]). The most frequently reported TEAEs of Grade 3 or 4 intensity were thrombocytopenia, lung infection and anemia. All Grade 3 or 4 TEAEs were well-balanced between the two groups; no categories had ≥10% difference, except anemia reported in 3 (7.7%) subjects in V(IV)d group and 8 (20%) in V(SC)d group.

Table 13: Most Common (at least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)	V(SC)d n (%)
Analysis set: safety	39	40
Total number of subjects with grade 3 or 4 TEAE	33 (84.6%)	33 (82.5%)
MedDRA system organ class/Preferred term		
Infections and infestations	18 (46.2%)	21 (52.5%)
Lung infection	9 (23.1%)	7 (17.5%)
Pneumonia	4 (10.3%)	4 (10.0%)
Upper respiratory tract infection	2 (5.1%)	3 (7.5%)
Bronchitis	2 (5.1%)	2 (5.0%)
Lower respiratory tract infection bacterial	0	2 (5.0%)
Pneumonia bacterial	2 (5.1%)	1 (2.5%)
Herpes zoster	3 (7.7%)	0
Blood and lymphatic system disorders	19 (48.7%)	17 (42.5%)
Thrombocytopenia	13 (33.3%)	12 (30.0%)
Anaemia	3 (7.7%)	8 (20.0%)
Neutropenia	5 (12.8%)	3 (7.5%)
Leukopenia	1 (2.6%)	2 (5.0%)
Lymphopenia	5 (12.8%)	2 (5.0%)
Leukocytosis	2 (5.1%)	0
Metabolism and nutrition disorders	8 (20.5%)	10 (25.0%)
Hypokalaemia	5 (12.8%)	5 (12.5%)
Hyponatraemia	2 (5.1%)	0
Gastrointestinal disorders	5 (12.8%)	5 (12.5%)
Diarrhoea	5 (12.8%)	3 (7.5%)
Nervous system disorders	7 (17.9%)	3 (7.5%)

Table 13: Most Common (at least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)	V(SC)d n (%)
Peripheral sensory neuropathy	5 (12.8%)	0
Eye disorders	2 (5.1%)	0
Cataract	2 (5.1%)	0

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone.
TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA version 20.0. Percentages are calculated with the number of subjects in each group as denominator.
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An overview of subjects with 1 or more treatment-emergent toxicity Grade 3 or 4 adverse events related to study treatment by MedDRA system organ class is presented in Table 14. Only Subject [redacted] in V(SC)d group reported one dexamethasone-related Grade 3 or 4 thrombocytopenia TEAE in the primary analysis was changed to unrelated in the final analysis. VELCADE or dexamethasone-related Grade 3 or 4 TEAEs were reported in 30 (76.9%) subjects in V[IV]d vs. 27 (67.5%) subjects in V[SC]d. The most frequently reported TEAEs were in the SOC of blood and lymphatic system disorders, followed by infections and infestations, and nervous system disorders. All Grade 3 or 4 TEAEs considered related to VELCADE were well-balanced between the two groups; no categories had ≥10% difference, except peripheral sensory neuropathy which was reported in 5 (12.8%) subjects in V(IV)d group only.

Table 14: Number of Subjects with 1 or More Treatment-emergent Toxicity Grade 3 or 4 Adverse Events Related to Study Treatment by MedDRA System Organ Class, Preferred Term and Relationship; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)			V(SC)d n (%)		
	Total	Related to VELCADE	Related to Dexa	Total	Related to VELCADE	Related to Dexa
Analysis set: safety	39			40		
Total number of subjects with grade 3 or 4 TEAE related to study treatment [a]	30 (76.9%)	28 (71.8%)	20 (51.3%)	27 (67.5%)	24 (60.0%)	20 (50.0%)
MedDRA system organ class/preferred term						
Blood and lymphatic system disorders	17 (43.6%)	16 (41.0%)	5 (12.8%)	15 (37.5%)	14 (35.0%)	2 (5.0%)
Thrombocytopenia	12 (30.8%)	12 (30.8%)	2 (5.1%)	12 (30.0%)	12 (30.0%)	0
Neutropenia	5 (12.8%)	5 (12.8%)	0	2 (5.0%)	2 (5.0%)	0
Lymphopenia	4 (10.3%)	2 (5.1%)	3 (7.7%)	2 (5.0%)	1 (2.5%)	1 (2.5%)
Anaemia	2 (5.1%)	2 (5.1%)	0	3 (7.5%)	3 (7.5%)	1 (2.5%)
Leukocytosis	1 (2.6%)	0	1 (2.6%)	0	0	0
Leukopenia	1 (2.6%)	1 (2.6%)	0	0	0	0
Infections and infestations	15 (38.5%)	11 (28.2%)	13 (33.3%)	16 (40.0%)	13 (32.5%)	15 (37.5%)
Lung infection	7 (17.9%)	4 (10.3%)	6 (15.4%)	5 (12.5%)	4 (10.0%)	5 (12.5%)
Pneumonia	4 (10.3%)	3 (7.7%)	3 (7.7%)	4 (10.0%)	4 (10.0%)	4 (10.0%)
Herpes zoster	3 (7.7%)	3 (7.7%)	3 (7.7%)	0	0	0
Bronchitis	2 (5.1%)	2 (5.1%)	2 (5.1%)	2 (5.0%)	2 (5.0%)	1 (2.5%)
Pneumonia bacterial	2 (5.1%)	0	2 (5.1%)	1 (2.5%)	0	1 (2.5%)
Upper respiratory tract infection	1 (2.6%)	1 (2.6%)	1 (2.6%)	0	0	0
Arthritis infective	0	0	0	1 (2.5%)	0	1 (2.5%)
Cellulitis orbital	0	0	0	1 (2.5%)	0	1 (2.5%)
Lower respiratory tract infection bacterial	0	0	0	2 (5.0%)	2 (5.0%)	2 (5.0%)

Table 14: Number of Subjects with 1 or More Treatment-emergent Toxicity Grade 3 or 4 Adverse Events Related to Study Treatment by MedDRA System Organ Class, Preferred Term and Relationship; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)			V(SC)d n (%)		
	Total	Related to VELCADE	Related to Dexa	Total	Related to VELCADE	Related to Dexa
Mumps	0	0	0	1 (2.5%)	1 (2.5%)	0
Pneumonia fungal	0	0	0	1 (2.5%)	0	1 (2.5%)
Nervous system disorders	6 (15.4%)	6 (15.4%)	1 (2.6%)	2 (5.0%)	2 (5.0%)	1 (2.5%)
Peripheral sensory neuropathy	5 (12.8%)	5 (12.8%)	1 (2.6%)	0	0	0
Neurotoxicity	1 (2.6%)	1 (2.6%)	0	1 (2.5%)	1 (2.5%)	1 (2.5%)
Neuropathy peripheral	0	0	0	1 (2.5%)	1 (2.5%)	0
Metabolism and nutrition disorders	5 (12.8%)	2 (5.1%)	4 (10.3%)	4 (10.0%)	0	4 (10.0%)
Hypokalaemia	4 (10.3%)	2 (5.1%)	3 (7.7%)	3 (7.5%)	0	3 (7.5%)
Diabetes mellitus	1 (2.6%)	0	1 (2.6%)	0	0	0
Hypocalcaemia	1 (2.6%)	1 (2.6%)	0	0	0	0
Hypophosphataemia	1 (2.6%)	1 (2.6%)	0	0	0	0
Hyperglycaemia	0	0	0	1 (2.5%)	0	1 (2.5%)
Gastrointestinal disorders	4 (10.3%)	4 (10.3%)	1 (2.6%)	5 (12.5%)	5 (12.5%)	3 (7.5%)
Diarrhoea	4 (10.3%)	4 (10.3%)	1 (2.6%)	3 (7.5%)	3 (7.5%)	1 (2.5%)
Dysbacteriosis	0	0	0	1 (2.5%)	1 (2.5%)	1 (2.5%)
Enteritis	0	0	0	1 (2.5%)	1 (2.5%)	1 (2.5%)
Flatulence	0	0	0	1 (2.5%)	1 (2.5%)	1 (2.5%)
Eye disorders	2 (5.1%)	1 (2.6%)	2 (5.1%)	0	0	0
Cataract	2 (5.1%)	1 (2.6%)	2 (5.1%)	0	0	0
Cardiac disorders	1 (2.6%)	1 (2.6%)	0	1 (2.5%)	1 (2.5%)	0
Cardiac failure	1 (2.6%)	1 (2.6%)	0	0	0	0
Palpitations	1 (2.6%)	1 (2.6%)	0	0	0	0
Ventricular arrhythmia	1 (2.6%)	1 (2.6%)	0	0	0	0
Sinus node dysfunction	0	0	0	1 (2.5%)	1 (2.5%)	0
Investigations	1 (2.6%)	1 (2.6%)	0	1 (2.5%)	0	1 (2.5%)
Gamma-glutamyltransferase increased	1 (2.6%)	1 (2.6%)	0	0	0	0
Blood pressure increased	0	0	0	1 (2.5%)	0	1 (2.5%)
Renal and urinary disorders	1 (2.6%)	1 (2.6%)	1 (2.6%)	0	0	0
Renal injury	1 (2.6%)	1 (2.6%)	1 (2.6%)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (2.6%)	1 (2.6%)	0	0	0	0
Asthma	1 (2.6%)	1 (2.6%)	0	0	0	0
Skin and subcutaneous tissue disorders	1 (2.6%)	1 (2.6%)	0	0	0	0
Dermatitis allergic	1 (2.6%)	1 (2.6%)	0	0	0	0

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone. TEAE = treatment-emergent adverse event. Dexa= dexamethasone.
[a] TEAEs of grade 3 or 4 related to at least 1 of the 2 study treatment: VELCADE and dexamethasone.
Note: Adverse events are reported using MedDRA version 20.0. Percentages are calculated with the number of subjects in each group as denominator.
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Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Deaths:

Table 15 presents a summary of death and causes of death for the safety population as of the 10 November 2018 cutoff date for the long-term extension. The total number of subjects who died during study increased from 11 (13.9%) at the primary analysis to 15 (19.0%) at the final analysis (primary/final in V(IV)d: 4 [10.3%] subjects/5 [12.8%] subjects; primary/final in V[SC]d: 7 [17.5%] subjects/10 [25.0%] subjects). Rates of death of all causes within 30 days of last dose, and within 60 days of first dose were

unchanged from rates presented in the primary CSR. Overall, a total of 4 (5.1%) subjects died within 30 days of last study treatment dose, of which 3 (7.7%) subjects were from V(IV)d group and 1 (2.5%) subject was from V(SC)d group. The three subjects in V(IV)d group died due to AEs unrelated to treatment (1 lung infection, 1 cardiopulmonary failure and 1 plasma cell myeloma).

TEAEs leading to death were reported in 5 subjects (3 [7.7%] in the V[IV]d and 2 [5.0%] in V[SC]d group) (Table 16), and were unchanged from this reported in the primary CSR. None of TEAEs (cardiopulmonary failure, plasma cell myeloma, lung infection) leading to deaths in V(IV)d group were related to the study treatment (VELCADE or dexamethasone). Both the 2 TEAEs (lung infection and pneumonia) leading to death in V(SC)d group were related to VELCADE and dexamethasone. An overview of these 2 subjects was summarized in primary CSR and details of the same are given in the Attachment Narratives.

Table 15: Summary of Death and Cause of Death; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)	V(SC)d n (%)	Total n (%)
Analysis set: safety	39	40	79
Total number of subjects who died during study	5 (12.8%)	10 (25.0%)	15 (19.0%)
Primary cause of death			
Adverse event	3 (7.7%)	3 (7.5%)	6 (7.6%)
At least one related[a]	0	2 (5.0%)	2 (2.5%)
AE(s) unrelated	3 (7.7%)	1 (2.5%)	4 (5.1%)
Disease progression	2 (5.1%)	4 (10.0%)	6 (7.6%)
Other	0	3 (7.5%)	3 (3.8%)
Total number of subjects who died within 30 days of last study treatment dose	3 (7.7%)	1 (2.5%)	4 (5.1%)
Primary cause of death			
Adverse event	3 (7.7%)	1 (2.5%)	4 (5.1%)
At least one related[a]	0	1 (2.5%)	1 (1.3%)
AE(s) unrelated	3 (7.7%)	0	3 (3.8%)
Disease progression	0	0	0
Other	0	0	0
Total number of subjects who died within 60 days of first study treatment dose	1 (2.6%)	1 (2.5%)	2 (2.5%)
Primary cause of death			
Adverse event	1 (2.6%)	1 (2.5%)	2 (2.5%)
At least one related[a]	0	1 (2.5%)	1 (1.3%)
AE(s) unrelated	1 (2.6%)	0	1 (1.3%)
Disease progression	0	0	0
Other	0	0	0

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone.
[a] Includes adverse events that were related to at least 1 of the 2 study treatment: VELCADE or dexamethasone.
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Table 16: Number of Subjects with 1 or More Treatment-emergent Adverse Event with Outcome Death by MedDRA Preferred Term and Relationship; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)			V(SC)d n (%)		
	Total	Related to VELCADE	Related to Dexa	Total	Related to VELCADE	Related to Dexa
Analysis set: safety	39			40		
Total number of subjects with TEAE with outcome death	3 (7.7%)	0	0	2 (5.0%)	2 (5.0%)	2 (5.0%)
MedDRA Preferred term						

Table 16: Number of Subjects with 1 or More Treatment-emergent Adverse Event with Outcome Death by MedDRA Preferred Term and Relationship; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d n (%)			V(SC)d n (%)		
	Total	Related to VELCADE	Related to Dexa	Total	Related to VELCADE	Related to Dexa
Lung infection	1 (2.6%)	0	0	1 (2.5%)	1 (2.5%)	1 (2.5%)
Pneumonia	0	0	0	1 (2.5%)	1 (2.5%)	1 (2.5%)
Cardiopulmonary failure	1 (2.6%)	0	0	0	0	0
Plasma cell myeloma	1 (2.6%)	0	0	0	0	0

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone. TEAE = treatment-emergent adverse event. Dexa = dexamethasone.
Note: Adverse events are reported using MedDRA version 20.0. Percentages are calculated with the number of subjects in each group as denominator.
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Serious Adverse Events:

The proportions of subjects who experienced at least 1 serious adverse event (55.0% and 61.5% of subjects in the V[SC]d and V[IV]d treatment groups, respectively), and considered by the investigator to be related to VELCADE or dexamethasone (53.8% and 50.0% of subjects in the V[SC]d and V[IV]d treatment groups, respectively) were unchanged from those reported in the primary CSR. For the long-term extension, this proportions can be found in Table 11, Overview of Treatment-Emergent Adverse Events. The most frequently reported serious adverse event, as discussed in Section 7.2.2.2 of the primary CSR, were lung infection (8 [20.5%] in V[IV]d vs. 5 [12.5%] in V[SC]d), pneumonia (6 [15.4%] vs. 3 [7.5%]), herpes zoster (2 [5.1%] vs. 0), thrombocytopenia (2 [5.1%] vs. 1 [2.5%]), peripheral sensory neuropathy (2 [5.1%] vs. 0), pneumonia bacterial (1 [2.6%] vs. 2 [5.0%]), bronchitis (0 vs. 2 [5.0%]), and lower respiratory tract infection bacterial (0 vs.2 [5.0%]), respectively.

Other Significant Adverse Events:

The proportions of TEAEs leading to study treatment discontinuation (30.8% and 25.0% of subjects in the V[SC]d and V[IV]d treatment groups, respectively), and TEAEs (all grades) that led to treatment cycle delays or dose modifications (79.5% and 65.0% of subjects in the V[SC]d and V[IV]d treatment groups, respectively) were unchanged from those reported in the primary CSR, Section 7.2.2.3. TEAEs leading to treatment discontinuation were well balanced between the two groups (no categories had $\geqslant$10% difference except peripheral sensory neuropathy only reported in 5 [12.8%] subjects in V[IV]d group). TEAEs (all grades) that led to treatment cycle delays or dose modifications were well-balanced between the two groups (no categories had $\geqslant$15% difference except peripheral sensory neuropathy (12 [30.8%] subjects in V[IV]d vs. 4 [10.0%] subjects in V[SC]d).

Adverse Events of Special Interest

Peripheral neuropathy:

Table 17 presents an overview for the safety population of subjects with 1 or more treatment-emergent peripheral neuropathy by MedDRA high level term, preferred term and maximum toxicity grade. The incidence of treatment-emergent peripheral neuropathy (PN) of any Grade was 24% higher in V(IV)d group compared with V(SC)d group (61.5% in V[IV]d vs. 37.5% in V[SC]d), was unchanged from that reported in the primary CSR. The incidence of Grade 2 PN events was 25.6% vs. 15.0%, and Grade 3 PN events was 12.8% vs. 2.5%, respectively. No subject experienced Grade 4 or higher treatment-emergent PN.

The MedDRA PT peripheral sensory neuropathy was reported in 21 (53.8%) subjects in V(IV)d and 9 (22.5%) in V(SC)d; and neuropathy peripheral and peripheral sensorimotor neuropathy were reported in 2 (5.1%) and 3 (7.5%), respectively. For subjects who experienced at least 1 PN, median time to first onset of PN were 2.64 months and 1.41 months, respectively. Among subjects who experienced at least 1 Grade ⩾3 PN, the median time to first onset of Grade ⩾3 PN were 2.79 months and 6.54 months, respectively (Attachment TSFAE10A). The values reported for the long-term extension were unchanged from those reported in the primary CSR.

Table 17: Number of Subjects with 1 or More Treatment-emergent Peripheral Neuropathy by MedDRA High Level Term, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d Toxicity Grade, n (%)						V(SC)d Toxicity Grade, n (%)					
	Total n (%)	1	2	3	4	5	Total n (%)	1	2	3	4	5
Analysis set: safety	39						40					
Total number of subjects with treatment emergent peripheral neuropathy	24 (61.5%)	9 (23.1%)	10 (25.6%)	5 (12.8%)	0	0	15 (37.5%)	8 (20.0%)	6 (15.0%)	1 (2.5%)	0	0
MedDRA high level term/preferred term												
Peripheral neuropathies NEC	24 (61.5%)	9 (23.1%)	10 (25.6%)	5 (12.8%)	0	0	15 (37.5%)	8 (20.0%)	6 (15.0%)	1 (2.5%)	0	0
Peripheral sensory neuropathy	21 (53.8%)	7 (17.9%)	9 (23.1%)	5 (12.8%)	0	0	9 (22.5%)	5 (12.5%)	4 (10.0%)	0	0	0
Neuropathy peripheral	2 (5.1%)	1 (2.6%)	1 (2.6%)	0	0	0	3 (7.5%)	2 (5.0%)	0	1 (2.5%)	0	0
Peripheral sensorimotor neuropathy	2 (5.1%)	2 (5.1%)	0	0	0	0	3 (7.5%)	1 (2.5%)	2 (5.0%)	0	0	0

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone.
Note: Adverse events are reported using MedDRA version 20.0. Percentages in the total column and toxicity grade columns are calculated with the number of subjects treated in each group as denominator.
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Cardiac Rhythm and Conduction Abnormalities, Heart Failure, Bleeding Events, and Herpes Zoster:

The events of cardiac rhythm and conduction abnormalities, heart failure, bleeding events, and herpes zoster were unchanged from those reported in the primary CSR, Section 7.2.2.4.

Hypotension, ADIP Disease, Pericardial Disease, CNS Disorders, and Tumor Lysis Syndrome:

No events of hypotensive, ADIP disease, pericardial disease, CNS disorders, and tumor lysis syndrome were reported in the study till the study was completed.

Assessment of Local Injection Site Tolerability

Table 18 presents an overview for the safety population of subjects with 1 or more treatment-emergent local injection site reactions that are reported as adverse events by MedDRA system organ class, preferred term and maximum toxicity grade. The events of LISRs were unchanged from those reported in the primary CSR, Section 7.2.2.5. None of the LISRs resulted in dose change or discontinuation, and all events recovered/resolved except for one subject with an unknown outcome due to withdrawal by subject.

Table 18: Number of Subjects with 1 or More Treatment-emergent Local Injection Site Reactions That Are Reported as Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d Toxicity Grade, n (%)						V(SC)d Toxicity Grade, n (%)					
	Total n (%)	1	2	3	4	5	Total n (%)	1	2	3	4	5
Analysis set: safety	39						40					
Total number of subjects with treatment-emergent local injection reactions reported as AE	4 (10.3%)	3 (7.7%)	1 (2.6%)	0	0	0	14 (35.0%)	13 (32.5%)	1 (2.5%)	0	0	0
MedDRA system organ class / preferred term												
General disorders and administration site conditions	3 (7.7%)	3 (7.7%)	0	0	0	0	8 (20.0%)	8 (20.0%)	0	0	0	0
Injection site rash	1 (2.6%)	1 (2.6%)	0	0	0	0	2 (5.0%)	2 (5.0%)	0	0	0	0
Injection site swelling	1 (2.6%)	1 (2.6%)	0	0	0	0	0	0	0	0	0	0
Local swelling	1 (2.6%)	1 (2.6%)	0	0	0	0	0	0	0	0	0	0
Injection site discolouration	0	0	0	0	0	0	1 (2.5%)	1 (2.5%)	0	0	0	0
Injection site erythema	0	0	0	0	0	0	4 (10.0%)	4 (10.0%)	0	0	0	0
Injection site hypersensitivity	0	0	0	0	0	0	1 (2.5%)	1 (2.5%)	0	0	0	0
Injection site pain	0	0	0	0	0	0	1 (2.5%)	1 (2.5%)	0	0	0	0
Vascular disorders	1 (2.6%)	0	1 (2.6%)	0	0	0	0	0	0	0	0	0
Phlebitis	1 (2.6%)	0	1 (2.6%)	0	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	0	0	7 (17.5%)	6 (15.0%)	1 (2.5%)	0	0	0
Erythema	0	0	0	0	0	0	7 (17.5%)	7 (17.5%)	0	0	0	0
Generalised erythema	0	0	0	0	0	0	1 (2.5%)	0	1 (2.5%)	0	0	0

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone.
Note: Adverse events are reported using MedDRA version 20.0. Percentages in the total column and toxicity grade columns are calculated with the number of subjects treated in each group as denominator.
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Clinical Laboratory Evaluation:

Laboratory Values over Time

A summary of worst toxicity grade during treatment in hematology and chemistry is presented in Table 19. One subject each in the V(SC)d treatment group previously categorized under hemoglobin high of Grade 0, and neutrophils low of Grade 0, now appeared under toxicity Grade 1. One subject in the V(SC)d treatment group previously categorized under albumin low of Grade 1 now appeared under toxicity Grade 2. The table is otherwise identical to that presented in the primary CSR.

Both hematology and chemistry laboratory abnormalities were generally similar on the 2 treatment arms, with the exception of platelets low (92.3% in V[IV]d vs. 70.0% in V[SC]d), and albumin low (55.3% vs.

76.9%, respectively) where more than 20.0% difference in the 2 groups was observed. In addition, V(SC)d group had 15% lower incidence in Grade 2 platelet low abnormality compared with V(IV)d group.

For both V(IV)d and V(SC)d groups, majority of subjects reported hemoglobin low of Grade 1 to 3 (89.7% vs. 92.5%) and platelets low of Grade 1 to 3 (84.6% vs. 65.0%) during the study for hematology laboratory. The most common biochemistry abnormalities during the study was albumin low of Grade 1 to 2 (55.3% vs. 76.9%).

Table 19: Summary of Worst Toxicity Grade during Treatment in Hematology and Biochemistry; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d Toxicity Grade, n (%)						V(SC)d Toxicity Grade, n (%)					
	Total n (%)	0	1	2	3	4	Total n (%)	0	1	2	3	4
Analysis set: safety	39						40					
Hematology												
WBC high (Leukocytosis)	39 (100.0%)	39 (100.0%)	0	0	0	0	40 (100.0%)	40 (100.0%)	0	0	0	0
WBC low (Leukopenia)	39 (100.0%)	24 (61.5%)	7 (17.9%)	7 (17.9%)	1 (2.6%)	0	40 (100.0%)	18 (45.0%)	10 (25.0%)	10 (25.0%)	1 (2.5%)	1 (2.5%)
Hemoglobin high	39 (100.0%)	36 (92.3%)	3 (7.7%)	0	0	0	40 (100.0%)	37 (92.5%)	3 (7.5%)	0	0	0
Hemoglobin low (Anemia)	39 (100.0%)	4 (10.3%)	19 (48.7%)	9 (23.1%)	7 (17.9%)	0	40 (100.0%)	3 (7.5%)	16 (40.0%)	10 (25.0%)	11 (27.5%)	0
Platelets low (Thrombocytopenia)	39 (100.0%)	3 (7.7%)	12 (30.8%)	11 (28.2%)	10 (25.6%)	3 (7.7%)	40 (100.0%)	12 (30.0%)	12 (30.0%)	5 (12.5%)	9 (22.5%)	2 (5.0%)
Neutrophils low (Neutropenia)	39 (100.0%)	23 (59.0%)	3 (7.7%)	6 (15.4%)	6 (15.4%)	1 (2.6%)	40 (100.0%)	23 (57.5%)	5 (12.5%)	9 (22.5%)	2 (5.0%)	1 (2.5%)
Biochemistry												
ALT high	38 (97.4%)	28 (73.7%)	10 (26.3%)	0	0	0	39 (97.5%)	29 (74.4%)	9 (23.1%)	1 (2.6%)	0	0
AST high	38 (97.4%)	30 (78.9%)	7 (18.4%)	1 (2.6%)	0	0	39 (97.5%)	28 (71.8%)	10 (25.6%)	1 (2.6%)	0	0
Creatinine high	38 (97.4%)	32 (84.2%)	4 (10.5%)	2 (5.3%)	0	0	39 (97.5%)	30 (76.9%)	6 (15.4%)	1 (2.6%)	0	2 (5.1%)
Sodium high (Hypernatremia)	38 (97.4%)	32 (84.2%)	6 (15.8%)	0	0	0	39 (97.5%)	34 (87.2%)	4 (10.3%)	1 (2.6%)	0	0
Sodium low (Hyponatremia)	38 (97.4%)	23 (60.5%)	11 (28.9%)	0	4 (10.5%)	0	39 (97.5%)	23 (59.0%)	14 (35.9%)	0	1 (2.6%)	1 (2.6%)
Potassium high (Hyperkalemia)	38 (97.4%)	36 (94.7%)	0	1 (2.6%)	1 (2.6%)	0	39 (97.5%)	38 (97.4%)	0	1 (2.6%)	0	0
Potassium low (Hypokalemia)	38 (97.4%)	27 (71.1%)	0	5 (13.2%)	3 (7.9%)	3 (7.9%)	39 (97.5%)	22 (56.4%)	0	10 (25.6%)	7 (17.9%)	0
Bilirubin high	38 (97.4%)	24 (63.2%)	11 (28.9%)	2 (5.3%)	1 (2.6%)	0	39 (97.5%)	27 (69.2%)	8 (20.5%)	4 (10.3%)	0	0
Alkaline phosphatase high	38 (97.4%)	26 (68.4%)	10 (26.3%)	2 (5.3%)	0	0	39 (97.5%)	27 (69.2%)	12 (30.8%)	0	0	0
Uric acid high (Hyperuricemia)	38 (97.4%)	24 (63.2%)	11 (28.9%)	0	0	3 (7.9%)	39 (97.5%)	19 (48.7%)	16 (41.0%)	0	0	4 (10.3%)

Table 19: Summary of Worst Toxicity Grade during Treatment in Hematology and Biochemistry; Safety Analysis Set (Study 26866138MMY3037)

	V(IV)d Toxicity Grade, n (%)						V(SC)d Toxicity Grade, n (%)					
	Total n (%)	0	1	2	3	4	Total n (%)	0	1	2	3	4
Corrected Calcium high (Hypercalcemia)	38 (97.4%)	33 (86.8%)	5 (13.2%)	0	0	0	39 (97.5%)	33 (84.6%)	4 (10.3%)	0	1 (2.6%)	1 (2.6%)
Corrected Calcium low (Hypocalcemia)	38 (97.4%)	29 (76.3%)	4 (10.5%)	5 (13.2%)	0	0	39 (97.5%)	26 (66.7%)	7 (17.9%)	5 (12.8%)	1 (2.6%)	0
Albumin low (Hypoalbuminemia)	38 (97.4%)	17 (44.7%)	15 (39.5%)	6 (15.8%)	0	0	39 (97.5%)	9 (23.1%)	19 (48.7%)	11 (28.2%)	0	0
Glucose high (Hyperglycemia)	38 (97.4%)	37 (97.4%)	0	0	1 (2.6%)	0	39 (97.5%)	36 (92.3%)	0	0	3 (7.7%)	0
Glucose low (Hypoglycemia)	38 (97.4%)	31 (81.6%)	6 (15.8%)	1 (2.6%)	0	0	39 (97.5%)	35 (89.7%)	3 (7.7%)	1 (2.6%)	0	0

Keys: V(IV)d= bortezomib (IV infusion)-dexamethasone; V(SC)d=bortezomib (SC infusion)-dexamethasone. WBC=White Blood Cell; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase.
Note: The laboratory toxicity grades are derived based on the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03. Grade 0 means normal. Subjects reported as Grade 0 are subjects with normal values or a value in the opposite direction (for laboratory tests with bidirectional toxicities defined). For each parameter, the total column includes all subjects with available data at both baseline and post-baseline, including those whose toxicity grade did not worsen during treatment; percentages in the total column are calculated with the number of treated subjects in each group as denominator. Percentages for toxicity grade columns are calculated with the number of subjects in the total column as denominator. For each subject and each parameter, the worst toxicity grade is selected.
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Other Safety Observations:

Other safety observations of vital signs and physical findings, electrocardiograms, ECOG performance status, and non-myeloma immunoglobulin assessments have no clinically relevant change compared to those reported in the primary CSR, Section 7.4.

Safety Summary:

With the exceptions of all-cause mortality, minimal additional safety data were generated after the 07 May 2018 data cutoff for the primary CSR. Not unexpectedly, with 6 months of additional follow-up, the overall rate of death was higher for the long-term extension (19.0%) than at the original analysis (13.9%) (Table 15 and primary CSR Section 7.2.2.1.).

Overall, the observed safety profile for the long-term extension was generally unchanged to that reported at the original analysis. Incidences of TEAEs, treatment-related TEAEs, Grade 3 or higher TEAEs, SAEs or TEAE leading to discontinuation of study treatment were similar between the V(IV)d and V(SC)d treatment groups.
Important difference noted between the treatment groups is a 24.0% difference in peripheral neuropathy events favoring the SC treatment group (37.5%) over the IV treatment group (61.5%) (Table 17).

MEDICAL RESOURCE UTILIZATION

No new medical resource utilization data were received for the long-term extension of Study MMY3037. Medical resource utilization is presented in Section 8 of the primary CSR.

CONCLUSIONS

This document provides pre-planned updated analyses of the Phase 3 Study MMY3037, a randomized, open-label, study designed to assess safety and efficacy of VELCADE SC as compared with VELCADE IV when administered in combination with low-dose dexamethasone in adult Chinese r/rMM subjects. The main purpose of the long-term extension analysis (10 November 2018 cutoff) was to provide an analysis on survival update. With 28 subjects in the V(IV)d treatment group and 24 subjects in the V(SC)d treatment group still in the study, and only 2 of the 24 subjects in the V(SC)d treatment group were still ongoing treatment at the original cutoff of 07 May 2018, new data were generated primarily for the long-term endpoints: TTP, PFS, 1-year survival, time to response/best response, duration of response, all-cause mortality, and outcomes of peripheral neuropathy events. Very few additional data were generated for overall best response and the adverse event profile.

The median duration of follow-up for the total ITT population was 15.97 months for the long-term extension versus 8.97 months reported in the primary CSR. The 1-year OS rate was still numerically higher in V(IV)d (89.3%) group as compared to V(SC)d (75.2%) group for the update, however the difference noted became smaller as compared with the primary analysis (75.2% in V[SC]d vs. 92.2% in V[IV]d, a difference of 17.0%). Updated results for other time-to-event endpoints (TTP, PFS, time to response/best response, and duration of response) were consistent with primary analyses as presented in the primary CSR. Except for one subject in the V(IV)d treatment group who improved from VGPR to CR, no changes were noted for updated analyses of overall best response.

After approximately 6 months of additional follow-up, the safety and tolerability profile of V(SC)d was generally comparable to V(IV)d with no new or unexpected side effects. Important differences which favored the V(SC)d group were observed, including a lower incidence of treatment-emergent PN (24.0%) compared to V(IV)d group (61.5% in V[IV]d vs. 37.5% in V[SC]d), was unchanged from that reported in the primary CSR. The incidence of Grade 2 PN events was 25.6% vs. 15.0%, and Grade 3 PN events was 12.8% vs. 2.5%, respectively.

The efficacy and safety results from the final analysis are consistent with those of the primary analysis and support SC route of VELCADE administration as an important alternative method for VELCADE IV treatment in Chinese subjects with relapsed or refractory multiple myeloma.

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1. Clinical Study Report 26866138MMY3037. A Phase 3, Randomized, Open-label Study of Subcutaneous and Intravenous VELCADE® in Combination with Dexamethasone in Chinese Subjects with Relapsed or Refractory Multiple Myeloma: Study 26866138-MMY3037 Pharmacokinetics, Efficacy, and Safety Data Summary. Xian Janssen Pharmaceutical Ltd (23 April 2018).
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JNJ-26866138-AAA (bortezomib)
Final Synoptic Clinical Study Report 26866138MMY3037

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STUDY TITLE:	A Phase 3, Randomized, Open-label Study of Subcutaneous and Intravenous VELCADE® in Combination with Dexamethasone in Chinese Subjects with Relapsed or Refractory Multiple Myeloma
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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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DATE: 7th May 2019

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Status: Approved, Date: 23 April 2019

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