1 Study Synopsis

Name of Sponsor/Company:	Janssen-Cilag International NV
Name of IMP:	Bortezomib (Velcade®)
Name of Active Ingredient:	Bortezomib
Protocol Number:	26866138MMY2036
Title of Study: A Phase II, Open-label Trial Using Velcade® for Re-treatment of Multiple Myeloma Subjects Following an Initial Response to Velcade®.	
Co-ordinating Investigator: There was no overall coordinating investigator for this study.	
Study Centres: Fifty-five study centres: 4 in Austria, 7 in Belgium, 5 in France, 11 in Germany, 6 in Greece, 7 in Italy, 1 in Luxembourg, 4 in Portugal and 10 in Spain.	
Publication (Reference): None.	
Studied Period: 12 Jun 2006 to 08 Jan 2010	**Phase of Development:** Phase II
Objectives: The primary objective of the study was to determine best response to bortezomib re-treatment in multiple myeloma subjects who had previously responded to a bortezomib based therapy. The secondary objectives of this study were to determine the incidence of serious adverse events (SAEs), Grade 3 and 4 adverse events (AEs), and all grades of neuropathy from each subject at baseline and every 6 weeks during treatment; to determine best confirmed myeloma protein (M-protein) response to bortezomib re-treatment in multiple myeloma subjects who had previously responded to bortezomib; and to determine the duration of response and time to progression. The exploratory objective of the study was to evaluate the investigator's best response relative to the best reported response to the previous course of treatment.	
Methodology: This study was an open-label, multicentre study designed to determine the efficacy and safety of re-treatment with bortezomib. Subjects were screened for eligibility up to 14 days before entering the treatment phase. Eligible subjects entered the treatment phase, defined as the period of time the subject received bortezomib, with or without dexamethasone. Subjects received up to 8 cycles of treatment, each lasting 3 weeks. The maximum number of cycles was dependent on subject response and investigator's discretion. It was recommended that subjects with a confirmed complete response (CR) would receive 2 cycles beyond a confirmation of CR. Subjects who did not achieve a CR but achieved a partial response (PR) received a total of 8 cycles. Subjects achieving no change (NC) in disease response (stable disease) could continue study treatment beyond 6 cycles, at the investigator's discretion, after discussion with the sponsor. All subjects attended an End of Treatment Visit. Subjects who completed treatment attended the End of Treatment Visit 30 to 42 days after receiving the last dose of bortezomib. Subjects who discontinued early from treatment and received systemic alternative anti-neoplastic therapy attended the End of Treatment Visit as soon as possible after discontinuation. After the End of Treatment Visit, all subjects who had responded with ≥NC entered long-term follow-up where they were required to visit the study centre every 2 months (8 weeks) until documented progressive disease (PD) or relapse, or until 1 year after administration of the last dose of study treatment to the last subject enrolled in the study, whichever was earlier. If PD was not documented during long-term follow-up, the subject was to attend the End of Study Visit as a final visit.	
Number of Subjects (Planned and Analysed): It was planned that approximately 125 subjects would be enrolled in the study. In total, 132 subjects were enrolled in the	

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study and 130 subjects were treated with bortezomib. In total, 126 subjects were included in the intention-to-treat (ITT) population and 130 subjects were included in the safety population.	
Diagnosis and Main Criteria for Inclusion: Male or female subjects aged ≥18 years with multiple myeloma who had previously tolerated 1.0 or 1.3 mg/m^2 bortezomib alone or in combination with other agents, had CR or PR upon completion of bortezomib therapy and either had PD if prior response to bortezomib was PR or had relapsed from CR. It was ≥6 months since their last dose of bortezomib and they had not received additional therapy for multiple myeloma, other than maintenance therapy with dexamethasone (or equivalent), thalidomide or interferon, or dexamethasone (or equivalent) as emergency therapy within 4 weeks before enrolment. Subjects had to have a Karnofsky performance status (KPS) score of ≥60 and an estimated life expectancy of >3 months at screening.	
Test Product, Dose and Mode of Administration, Batch Number: Subjects received bortezomib (Batch Numbers 354253 and 350251) intravenously twice a week, on Days 1, 4, 8 and 11 of each cycle. There were at least 72 h between doses. The initial bortezomib dose was the last tolerated dose (1.0 or 1.3 mg/m^2) on the previous bortezomib-based treatment. At the investigator's discretion, subjects could have received bortezomib in combination with dexamethasone, in accordance with the standard of care.	
Duration of Treatment: Subjects received up to 8 cycles; each cycle was 3 weeks long. Subjects were followed up approximately 6 weeks after receiving the last dose of bortezomib. Subjects who responded with a ≥NC entered long-term follow-up for 1 year after administration of the last dose of study treatment or until documented PD, whichever was earlier. The median (range) duration of the study (measured over both the treatment and follow-up phases of the study) was 30.4 (0 to 100) weeks. The median (range) follow-up period was 13.3 (3 to 84) months.	
Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable.	
Criteria for Evaluation:	
Efficacy: The primary efficacy variable was defined as the best confirmed response on treatment as assessed according to the European Group for Blood and Marrow Transplantation (EBMT) criteria. As supportive analyses to the primary endpoint, the single best response during the treatment period was analysed, as well as the best confirmed and single best responses based on serum or urine M-protein data. The secondary efficacy variables were: • M-protein response rates for best confirmed and single best responses. • Time to progression for best confirmed (TTP) and single best (TTP_BS) responses. • Duration of response for best confirmed (DOR) and single best (DOR_BS) responses. • Time to response for best confirmed (TTR), single best (TTR_BS) and single first (TTR_F) responses. • Best response comparison.	

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Exploratory efficacy variables were:

- Treatment free interval (TFI).
- Time to next therapy re-treatment (TTNTR).
- Time to next therapy for both bortezomib lines (TTNTB).

Other efficacy variables were:

- KPS.
- The additional concerns section of the Functional Assessment of Cancer Therapy/Gynaenocologic Oncology Group Neurotoxicity (FACT/GOG-Ntx) questionnaire.
- Bone marrow aspirations/biopsy and/or skeletal surveys (X-rays).

Safety: Safety was assessed by the monitoring of AEs, physical examination (complete or symptom-directed), vital signs measurements (heart rate, respiratory rate, and blood pressure), weight, body surface area, and clinical laboratory tests (haematology and serum chemistry).

Statistical Methods: All analyses were performed according to the independent Data Monitoring Committee review and for the ITT population, unless otherwise specified.

Primary, Primary (Supportive) and Primary (Subgroup) Efficacy Analyses: The proportions of subjects with best confirmed and single best responses, overall and based only on serum or urine M-protein data, in each of the disease response categories, together with the CR and PR responses combined and the CR, PR and minimal response (MR) responses combined, were presented with their associated 2-sided exact 95% confidence intervals (CIs). The exact CIs were calculated using the Clopper-Pearson method. The primary analyses were also presented by the following subgroups: number of prior therapies, administered therapy (bortezomib monotherapy or bortezomib with dexamethasone), age, previous stem cell transplant and/or thalidomide therapy and starting bortezomib dose. These analyses were for end of treatment.

As an additional analysis, the number and percentage of subjects with negative serum and urine values throughout the study who had immunofixation and/or bone marrow data collected at the corresponding visit were presented.

Secondary Efficacy Analyses: For the best confirmed and single best M-protein response rates, the number and percentage of subjects in each response category were presented together with their associated 2-sided exact 95% CIs at the end of the study. The exact CIs were calculated using the Clopper-Pearson method.

Kaplan-Meier analyses were used to estimate the distributions of the following:

- TTP and TTP_BS for subjects with confirmed responses of ≥PR and separately for those with responses of ≥NC over the duration of the study. These analyses were also presented by number of previous therapies, age and, as an additional analysis, administered therapy (bortezomib monotherapy or bortezomib with dexamethasone). Also as an additional analysis, TTP in previous therapy was calculated.
- DOR and DOR_BS for subjects achieving either a CR or PR over the duration of the study. These analyses were also presented by number of previous therapies, age and, as an additional analysis, administered therapy (bortezomib monotherapy or bortezomib with dexamethasone). Also as an additional

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analysis, DOR in previous therapy was calculated.

- TTR, TTR_BS and TTR_F for subjects with responses of CR or PR and responses of CR, PR or MR at the End of Treatment only. These analyses were also presented by administered therapy (bortezomib monotherapy or bortezomib with dexamethasone).

Best response comparison results were presented categorically using shift tables.

Exploratory Efficacy Analyses: For subjects with a best confirmed response of CR, PR, MR or NC, Kaplan-Meier analyses were used to analyse TFI, TTNTR and TTNTB at the end of the study only.

Other Efficacy Analyses: KPS results were summarised using descriptive statistics. FACT/GOG-Ntx data were analysed as weighted sums and the results were listed only. Skeletal survey (X-ray) and bone marrow aspirations/biopsies were listed only.

Safety Analyses: Safety evaluation was primarily based on the incidence, intensity and type of neuropathy Grade 3 and 4 AEs and SAEs in subjects who received any amount of study drug. The intesity of AEs was determined with reference to the National Cancer Institute (NCI) Common Terminology Criteria of AEs (v3.0). Treatment emergent AEs (TEAEs) were coded using Medical Dictionary for Regulatory Activities (v9.0) by system organ class and preferred term.

Kaplan-Meier analyses were used to estimate the distribution of the time to resolution and time to improvement of peripheral neuropathy (PN) events. Time to onset of first PN event was estimated as an additional analysis. Clinical laboratory tests, vital signs measurements, weight and body surface area data were summarised using descriptive statistics. Physical examination results were presented categorically using shift tables.

Summary – Conclusions:

Demography and Baseline Data: The mean (standard deviation [SD]) age and body surface area of the subjects were 66.9 (9.8) years and 1.789 (0.191) m^2, respectively. The majority of subjects were male (74 [56.9%] subjects) and Caucasian (127 [97.7%] subjects).

The most frequently reported KPS score was 90 (51 [39.2%] subjects), followed by 80 (29 [22.3%] subjects) and 100 (28 [21.5%] subjects).

The proportion of subjects who had received 2 prior lines of therapy (including bortezomib) for multiple myeloma (80 [61.5%] subjects) was much higher than the proportion of subjects who had received 1, 3 or ≥4 prior lines of therapy (15 [11.5%] subjects, 23 [17.7%] subjects and 12 [9.2%] subjects, respectively). The mean (SD) number of prior lines of therapy received was 2.3 (1.0).

For the majority of subjects, previous bortezomib therapy was received in combination with another therapy (82 [63.1%] subjects). The mean (SD) duration of previous bortezomib therapy was 5.1 (2.9) months and the mean (SD) time from the previous bortezomib therapy to the first dose of bortezomib in this study was 15.7 (7.5) months. The majority of subjects had received >3 cycles of previous bortezomib therapy (117 [90.0%] subjects).

For the majority of subjects, the best response on previous bortezomib therapy was a partial response (96 [73.8%] subjects). The median (range) time to relapse/achieve PD was 17.691 (4.27-41.43) months.

Based on the additional concerns section of the FACT/GOG-Ntx questionnaire, 94 (72.3%) subjects had symptoms of peripheral neuropathy at baseline.

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Efficacy Results:

Primary Analysis: In accordance with the EBMT criteria, the proportions of subjects in each of the best confirmed response categories are given below (N=126):

- CR: 1 (0.8%) subject.
- PR: 49 (38.9%) subjects.
- ≥PR: 50 (39.7%) subjects.
- MR: 23 (18.3%) subjects.
- ≥MR: 73 (57.9%) subjects.
- NC: 14 (11.1%) subjects.
- PD: 12 (9.5%) subjects.
- Unknown/unable to assess: 27 (21.4%) subjects.

Results by subgroup are presented under 'Primary Endpoint and Primary Supportive Analyses – Subgroup Analyses' below. Results by single best prior response are presented under 'Secondary Endpoints'/'Best Response Comparison' below.

As an additional analysis, 35 (27.8%) subjects had a negative serum and urine M-protein result at some point during the study. Of these 35 subjects, no subjects had both immunofixation and bone marrow data present at the visit corresponding with negative serum and urine. Two (5.71%) subjects had immunofixation data present, 6 (17.1%) subjects had a bone marrow aspiration result present, and 3 (8.57%) subjects had a bone marrow biopsy result present.

Primary Supportive Analyses (Overall): Overall results for single best response were generally better than those for best confirmed response; the proportions of subjects in each of the single best response categories are given below (N=126):

- CR: 1 (0.8%) subject.
- PR: 68 (54.0%) subjects.
- ≥PR: 69 (54.8%) subjects.
- MR: 25 (19.8%) subjects.
- ≥MR: 94 (74.6%) subjects.
- NC: 16 (12.7%) subjects.
- PD: 7 (5.6%) subjects.
- Unknown/unable to assess: 9 (7.1%) subjects.

Overall results for best confirmed serum response and single best serum response were generally similar to those for best confirmed response.

Overall results for best confirmed urine response were generally worse than those for best confirmed response; the proportions of subjects in each of the response categories are given below (N=126):

- CR: 1 (0.8%) subject.
- PR: 17 (13.5%) subjects.
- ≥PR: 18 (14.3%) subjects.
- MR: 8 (6.3%) subjects.
- ≥MR: 26 (20.6%) subjects.
- NC: 11 (8.7%) subjects.
- PD: 7 (5.6%) subjects.
- Unknown/unable to assess: 82 (65.1%) subjects.

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Overall results for single best urine response were generally worse than those for best confirmed response; the proportions of subjects in each of the response categories are given below (N=126):

- CR: 1 (0.8%) subject.
- PR: 27 (21.4%) subjects.
- ≥PR: 28 (22.2%) subjects.
- MR: 13 (10.3%) subjects.
- ≥MR: 41 (32.5%) subjects.
- NC: 9 (7.1%) subjects.
- PD: 4 (3.2%) subjects.
- Unknown/unable to assess: 72 (57.1%) subjects.

Results for urine were mainly affected by the large proportions of subjects whose responses were unknown/unable to assess.

Primary Endpoint and Primary Supportive Analyses – Subgroup Analyses: Conclusions for urine are not given for the subgroup analyses below because results for urine were mainly affected by the large proportions of subjects whose responses were unknown/unable to assess (see results under 'Primary Supportive Analyses [Overall]' above).

Number of prior lines of therapy subgroups: The proportion of subjects with a best confirmed response of ≥PR appeared to decrease as the number of prior lines of therapy increased. The proportions of subjects with a best confirmed response of ≥MR were similar for subjects who had received 1, 2 or 3 prior lines of therapy, and smaller for subjects who had received ≥4 prior lines of therapy. The proportions of subjects with best confirmed responses of ≥PR and ≥MR for each subgroup are given below:

- 1 prior line of therapy: ≥PR: 10 (66.7%) subjects; ≥MR: 10 (66.7%) subjects.
- 2 prior lines of therapy: ≥PR: 30 (38.5%) subjects; ≥MR: 45 (57.7%) subjects.
- 3 prior lines of therapy: ≥PR: 7 (33.3%) subjects; ≥MR: 13 (61.9%) subjects.
- ≥4 prior lines of therapy: ≥PR: 3 (25.0%) subjects; ≥MR: 5 (41.7%) subjects.

Number of prior lines of therapy subgroup results for single best response, best confirmed serum response and single best serum response were generally similar to those for best confirmed response.

Administered therapy (bortezomib monotherapy or bortezomib with dexamethasone) subgroups: The proportions of subjects with a best confirmed response of ≥PR, and ≥MR appeared to be greater for subjects who received bortezomib with dexamethasone compared with those who received bortezomib monotherapy. The proportions of subjects with best confirmed responses of ≥PR and ≥MR for each subgroup are given below (N=126):

- Bortezomib with dexamethasone: ≥PR: 39 (42.4%) subjects; ≥MR: 58 (63.0%) subjects.
- Bortezomib monotherapy: ≥PR: 11 (32.4%) subjects; ≥MR: 15 (44.1%) subjects.

Administered therapy (bortezomib monotherapy or bortezomib with dexamethasone) subgroup results for single best response, best confirmed serum response and single best serum response were generally similar to those for best confirmed response.

Age subgroups: The proportion of subjects with a best confirmed response of ≥PR

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appeared to be greater for younger subjects (aged ≤65 years) compared with older subjects (aged >65 years). There was no apparent difference between the 2 age subgroups in the proportion of subjects with a best confirmed response of ≥MR. The proportions of subjects with best confirmed responses of ≥PR and ≥MR for each subgroup are given below:

- Aged ≤65 years: ≥PR: 24 (45.3%) subjects; ≥MR: 31 (58.5%) subjects.
- Aged >65 years: ≥PR: 26 (35.6%) subjects; ≥MR: 42 (57.5%) subjects.

Age subgroup results for single best response, best confirmed serum response and single best serum response were generally not similar to those for best confirmed response. Results showed either no apparent difference between the 2 age subgroups (single best response for responses of ≥PR and ≥MR, and best confirmed serum response for responses of ≥PR), or the proportions of subjects having responses of ≥PR and/or ≥MR in the younger age subgroup appeared to be slightly smaller than the proportions in the older age subgroup:

- The proportions of subjects with best confirmed serum responses ≥MR were 24 (45.3%) subjects and 39 (53.4%) subjects in the younger and older age subgroups, respectively.
- The proportions of subjects with single best serum responses ≥PR were 21 (39.6%) subjects and 36 (49.3%) subjects in the younger and older age subgroups, respectively.
- The proportions of subjects with single best serum responses ≥MR were 26 (49.1%) subjects and 51 (69.9%) subjects in the younger and older age subgroups, respectively.

Prior therapy with thalidomide or stem cell transplant subgroups: The proportions of subjects with best confirmed responses of ≥PR and ≥MR for each subgroup are given below:

- Thalidomide only: ≥PR: 8 (33.3%) subjects; ≥MR:13 (54.2%) subjects.
- Stem cell transplant only: ≥PR: 10 (41.7%) subjects; ≥MR: 16 (66.7%) subjects.
- Both therapies: ≥PR: 1 (7.7%) subject; ≥MR: 4 (30.8%) subjects.
- Neither therapy: ≥PR: 31 (47.7%) subjects; ≥MR: 40 (61.5%) subjects.

Prior therapy subgroup results for single best response, best confirmed serum response and single best serum response were generally similar to those for best confirmed response.

Starting dose of bortezomib subgroups: The proportions of subjects with best confirmed responses of ≥PR, and ≥MR appeared to be slightly greater (≥PR and ≥MR) for subjects with the higher starting dose of 1.3 mg/m^2 bortezomib compared with those with the lower starting dose of ≤1.0 mg/m^2 bortezomib. The proportions of subjects with best confirmed responses of ≥PR and ≥MR for each subgroup are given below:

- ≤1.0 mg/m^2 bortezomib: ≥PR: 12 (35.3%) subjects; ≥MR: 16 (47.1%) subjects.
- 1.3 mg/m^2 bortezomib: ≥PR: 38 (41.3%) subjects; ≥MR: 57 (62.0%) subjects.

Starting dose of bortezomib subgroup results for single best response, best confirmed serum response and single best serum response were not similar to those for best confirmed response. Results generally showed either no apparent difference between the 2 starting dose subgroups (single best response for responses of ≥PR and ≥MR, and single best serum response for responses of ≥MR), or there appeared to be

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slightly smaller proportions of subjects having responses of ≥PR and/or ≥MR in the higher starting dose of bortezomib subgroup compared with the lower starting dose of bortezomib subgroup:

- The proportions of subjects with best confirmed serum responses ≥PR were 31 (33.7%) subjects and 14 (41.2%) subjects in the higher and lower starting dose of bortezomib subgroups, respectively.
- The proportions of subjects with single best serum responses ≥PR were 39 (42.4%) subjects and 18 (52.9%) subjects in the higher and lower starting dose of bortezomib subgroups, respectively.

(The proportions of subjects with best confirmed serum responses ≥MR were 47 [51.1%] subjects and 16 [47.1%] subjects in the higher and lower starting dose of bortezomib subgroups, respectively.)

Secondary Endpoints:

Serum M-protein Response Rate: The proportions of subjects in each serum M-protein best confirmed response category were as follows:

- 100% decrease: 21 (16.7%) subjects.
- ≥90% to <100% decrease: 0 subjects.
- ≥75% to <90% decrease: 3 (2.4%) subjects.
- ≥50% to <75% decrease: 20 (15.9%) subjects.
- ≥25% to <50% decrease: 16 (12.7%) subjects.
- ≥-25% to 25% (no change): 10 (7.9%) subjects.
- <-25% decrease: 10 (7.9%) subjects.
- Missing: 27 (21.4%) subjects.
- Not evalulable (<5 g/L): 19 (15.1%) subjects.

Results for serum M-protein single best response were similar to those for serum M-protein best confirmed response.

Urine M-protein Response Rate:

The proportions of subjects in each urine M-protein best confirmed response category were as follows:

- 100% decrease: 18 (14.3%) subjects.
- ≥90% to <100% decrease: 3 (2.4%) subjects.
- ≥75% to <90% decrease: 4 (3.2%) subjects.
- ≥50% to <75% decrease: 6 (4.8%) subjects.
- ≥25% to <50% decrease: 4 (3.2%) subjects.
- ≥-25% to 25% (no change): 6 (4.8%) subjects.
- <-25% decrease: 9 (7.1%) subjects.
- Missing: 53 (42.1%) subjects.
- Not evalulable (<200 mg/24 h): 23 (18.3%) subjects.

Results for the urine M-protein single best response were similar to those for urine M-protein best confirmed response.

Time to Progression:

Median (95% CI) results for TTP (based on best confirmed responses in this study) are given below. (Results for TTP in previous study and TTP in the current study can not be compared directly because the methodologies used to generate them were not the

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- TTP in previous study (≥PR; no censoring): 18.87 (15.41, 21.55) months.
- TTP in previous study (≥NC; no censoring): 18.04 (15.90, 19.68) months.
- TTP (≥PR; 16 of 50 [32.0%] subjects censored): 8.38 (7.88, 9.72) months.
- TTP (≥NC; 27 of 87 [31.0%] subjects censored): 7.92 (6.70, 8.38) months.

There was no apparent effect of number of prior lines of therapy on TTP for subjects with best confirmed responses of ≥PR and ≥NC. Median (95% CI) TTP results for each subgroup were as follows:

- 1 prior line of therapy: ≥PR: 8.36 (6.57, 10.84) months.
  ≥NC: 7.00 (6.57, 10.84) months.
- 2 prior lines of therapy: ≥PR: 9.00 (7.92, 10.15) months.
  ≥NC: 8.05 (7.13, 9.07) months.
- 3 prior lines of therapy: ≥PR: 6.70 (5.09, 8.84) months.
  ≥NC: 6.70 (5.09, 7.56) months.
- ≥4 prior lines of therapy: ≥PR: 8.74 (8.38, 10.32) months.
  ≥NC: 8.38 (4.17, 10.32) months.

There was no apparent effect of administered therapy (bortezomib monotherapy or bortezomib with dexamethasone) on TTP for subjects with best confirmed responses of ≥PR and ≥NC. Median (95% CI) TTP results for each subgroup were as follows:

- Bortezomib with dexamethasone: ≥PR: 8.38 (7.00, 9.72) months.
  ≥NC: 7.88 (6.70, 8.74) months.
- Bortezomib monotherapy: ≥PR: 8.44 (7.92, 14.78) months.
  ≥NC: 7.92 (6.24, 10.12) months.

For subjects with a best confirmed response of ≥PR, subjects in the older subgroup appeared to have a slightly longer median (95% CI) TTP compared with those in the younger subgroup. However, for subjects with a best confirmed response of ≥NC, there was no apparent difference between age subgroups in median (95% CI) TTP. Median (95% CI) TTP results for each subgroup were as follows:

- Aged ≤65 years: ≥PR: 7.92 (7.00, 10.15) months.
  ≥NC: 7.92 (6.34, 8.84) months.
- Aged >65 years: ≥PR: 8.74 (8.05, 10.12) months.
  ≥NC: 7.56 (6.70, 8.74) months.

Time to Progression for Single Best Response: TTP_BS results were generally similar to those for TTP with the following exceptions:

- For subjects with a single best response of ≥PR only, subjects who received bortezomib monotherapy appeared to have a slightly longer median (95% CI) TTP_BS than those who received bortezomib with dexamethasone:
  - Bortezomib monotherapy: 8.44 (7.92, 18.43) months.
  - Bortezomib with dexamethasone: 7.88 (6.57, 8.74) months.
- There was no apparent effect of age subgroup on TTP_BS for subjects with a single best response of ≥PR.

Duration of Response:

Median (95% CI) results for DOR (based on best confirmed responses in this study) are given below. (Results for DOR in previous study and DOR in the current study can not be compared directly because the methodologies used to generate them were not

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- DOR in previous study (≥PR; no censoring): 13.37 (10.64, 16.03) months.
- DOR (≥PR; 16 of 50 [32.0%] subjects censored): 6.50 (4.96, 7.06) months.

There was no apparent effect of number of prior lines of therapy on DOR for subjects with a best confirmed response of ≥PR. Median (95% CI) DOR results for each subgroup were as follows:

- 1 prior line of therapy: ≥PR: 5.58 (3.68, 9.46) months.
- 2 prior lines of therapy: ≥PR: 6.67 (5.35, 8.74) months.
- 3 prior lines of therapy: ≥PR: 4.89 (3.84, 5.09) months.
- ≥4 prior lines of therapy: ≥PR: 7.10 (7.00, 8.77) months.

Subjects who received bortezomib monotherapy appeared to have a slightly longer median (95% CI) DOR compared with those who received bortezomib with dexamethasone. Median (95% CI) DOR results for each subgroup were as follows:

- Bortezomib with dexamethasone: ≥PR: 6.47 (4.70, 7.00) months.
- Bortezomib monotherapy: ≥PR: 7.06 (5.35, 10.64) months.

Subjects in the older subgroup appeared to have a slightly longer DOR compared with those in the younger subgroup. Median (95% CI) DOR results for each subgroup were as follows:

- Aged ≤65 years: ≥PR: 5.35 (4.07, 6.80) months.
- Aged >65 years: ≥PR: 7.00 (4.89, 8.74) months.

Duration of Single Best Response: DOR_BS was similar to DOR. Among the 69 subjects assessed who had a single best response of ≥PR, the median (95% CI) DOR_BS was 6.18 (4.89, 6.96) months.

There was no apparent effect of number of prior lines of therapy on DOR_BS for subjects with a single best response of ≥PR. Median (95% CI) DOR_BS results for each subgroup were as follows:

- 1 prior line of therapy: ≥PR: 5.58 (3.81, not calculable) months.
- 2 prior lines of therapy: ≥PR: 6.54 (4.14, 7.95) months.
- 3 prior lines of therapy: ≥PR: 4.80 (3.58, 5.09) months.
- ≥4 prior lines of therapy: ≥PR: 7.10 (7.00, 8.77) months.

Subjects who received bortezomib monotherapy appeared to have a slightly longer DOR_BS compared with those who received bortezomib with dexamethasone. Median (95% CI) DOR_BS results for each subgroup were as follows:

- Bortezomib with dexamethasone: ≥PR: 5.35 (4.14, 6.80) months.
- Bortezomib monotherapy: ≥PR: 7.06 (5.35, 16.20) months.

There was no apparent effect of age subgroup on DOR_BS for subjects with a single best response of ≥PR. Median (95% CI) DOR_BS results for each subgroup were as follows:

- Aged ≤65 years: ≥PR: 5.35 (4.83, 6.80) months.
- Aged >65 years: ≥PR: 6.67 (3.84, 7.95) months.

Time to Best Confirmed Response: The median (95% CI) TTR was not calculable for subjects with a best confirmed response of ≥PR because there were insufficient data to estimate the median time to achieve a ≥PR event, and was 2.89 (2.79, 4.27) months for subjects with a best confirmed response of ≥MR.

There was no apparent effect of administered therapy (bortezomib monotherapy or

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bortezomib with dexamethasone) on TTR for subjects with a best confirmed response of ≥PR; however, when MR was included, median (95% CI) TTR appeared to be shorter for subjects who received bortezomib with dexamethasone compared with subjects who received bortezomib monotherapy. Median (95% CI) TTR results for each subgroup were as follows:

- Bortezomib with dexamethasone: ≥PR: not calculable because of insufficient data.
  ≥MR: 2.79 (1.87, 4.17) months.
- Bortezomib monotherapy: ≥PR: not calculable because of insufficient data.
  ≥MR: 4.17 (2.79, not calculable) months.

Time to Single Best Response: The median (95% CI) TTR_BS was 3.42 (2.56, 4.89) months for subjects with a single best response of ≥PR and 1.87 (1.61, 2.79) months for subjects with a single best response of ≥MR.

Median (95% CI) TTR_BS appeared to be shorter for subjects who received bortezomib with dexamethasone compared with subjects who received bortezomib monotherapy. Median (95% CI) TTR_BS results for each subgroup were as follows:

- Bortezomib with dexamethasone: ≥PR: 3.02 (1.87, 4.89) months.
  ≥MR: 1.64 (1.54, 2.10) months.
- Bortezomib monotherapy: ≥PR: 4.17 (2.79, not calculable) months.
  ≥MR: 2.79 (1.54, 4.17) months.

Time to First Response: The median (95% CI) TTR_F was 1.64 (1.61, 2.10) months for subjects with a single first response of ≥PR and 1.51 (1.45, 1.58) months for those with a single first response of ≥MR.

There was generally no apparent effect of administered therapy (bortezomib monotherapy or bortezomib with dexamethasone) on TTR_F for subjects with single best responses of ≥PR and of ≥MR. Median (95% CI) TTR_F results for each subgroup were as follows:

- Bortezomib with dexamethasone: ≥PR: 1.68 (1.64, 2.10) months.
  ≥MR: 1.51 (1.41, 1.64) months.
- Bortezomib monotherapy: ≥PR: 1.54 (1.45, not calculable) months.
  ≥MR: 1.45 (1.45, 1.54) months.

Best Response Comparison: Among the 32 subjects who responded to initial bortezomib treatment achieving a CR, 1 (3.1%) subject, 19 (59.4%) subjects, 4 (12.5%) subjects, 6 (18.8%) subjects, 1 (3.1%) subject, no subjects and 1 (3.1%) subject achieved single best responses of CR, PR, MR, NC, PD, relapse from CR and unknown/unable to assess in this study, respectively. Among the 94 subjects who responded to initial bortezomib treatment achieving a PR, no subjects, 49 (52.1%) subjects, 21 (22.3%) subjects, 10 (10.6%) subjects 6 (6.4%) subjects, no subjects and 8 (8.5%) subjects achieved single best responses of CR, PR, MR, NC, PD, relapse from CR and unknown/unable to assess in this study, respectively:

Single best response on study: Best prior response of CR (N=32) or PR (N=94) (n [%]):

CR:	CR: 1 (3.1);	PR: 0.
PR:	CR: 19 (59.4);	PR: 49 (52.1).
MR:	CR: 4 (12.5);	PR: 21 (22.3).

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NC:	CR: 6 (18.8);	PR: 10 (10.6).
PD:	CR: 1 (3.1);	PR: 6 (6.4).
Relapse from CR:	CR: 0;	PR: 0.
Unknown/unable to assess:	CR: 1 (3.1);	PR: 8 (8.5).

Subjects who previously received bortezomib in combination with other agents and had a previous best response of CR appeared to achieve a higher proportion of PR responses in this study compared with subjects who previously received bortezomib monotherapy and had a previous best response of CR (13 [72.2%] subjects and 6 [42.9%] subjects, respectively). Subjects who previously received bortezomib in combination with other agents and had a previous best response of PR also generally appeared to achieve a higher proportion of PR responses in this study compared with subjects who previously received bortezomib monotherapy and had a previous best response of PR, although the differences appeared to be smaller than they did for previous best responses of CR (34 [54.8%] subjects and 15 [46.9%] subjects, respectively).

Exploratory Endpoints:

Treatment Free Interval: Median (95% CI) TFI was not calculable because the median was not reached; TFI ranged from 0.2 to 25.3 months. When analysed by best confirmed response individually, median (95% CI) TFI was not calculable because the median was not reached for CR (1 subject; TFI = 17.7 months) and NC (14 subjects; TFI ranged from 0.2 to 25.3 months). Subjects with a best confirmed response of PR had a longer median (95% CI) TFI than those with a best confirmed response of MR (9.82 [9.82, not calculable] months and 5.68 [4.53, not calculable] months, respectively). The median (range) follow-up period for the study was 13.3 (3 to 84) months.

Time to Next Treatment Re-treatment: Median (95% CI) TTNTR was not calculable because the median was not reached; TTNTR ranged from 3.3 to 28.2 months. When analysed by best confirmed response individually, median (95% CI) TTNTR was also not calculable for CR, PR and NC because the medians were not reached for CR (1 subject; TFI = 20.7 months), PR (49 subjects; TTNTR ranged from 3.3 to 18.7 months) or NC (14 subjects; TTNTR ranged from 3.4 to 28.2 months). Subjects with a best confirmed response of MR had a median (95% CI) TTNTR of 10.84 (8.31, not calculable) months. The median (range) follow-up period for the study was 13.3 (3 to 84) months.

Time to Next Therapy Both Bortezomib Lines: Median (95% CI) TTNTB was not calculable for TTNTB overall (TTNTB ranged from 16.2 to 62.8 months) or for any of the best confirmed response categories (CR: 1 subject, TTNTB = 62.8 months; PR: 49 subjects, TTNTB ranged from 16.6 to 54.3 months; MR: 23 subjects, TTNTB ranged from 16.2 to 54.2 months; NC: 14 subjects, TTNTB ranged from 17.3 to 57.2 months) because the medians were not reached. The median (range) follow-up period for the study was 13.3 (3 to 84) months.

Other Efficacy Assessments:

Karnofsky Performance Status Score: There were no notable mean changes from baseline in KPS score during the study.

FACT/GOG-Ntx Questionnaire and Skeletal Surveys and Bone Marrow Assessments: These data were listed only.

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Safety Results: In total, 10 subjects died: 8 [6.2%] subjects had TEAEs leading to death and 2 subjects died during follow-up or more than 30 days after the last dose of study treatment. The most frequently reported TEAE leading to death was disease progression (2 [1.5%] subjects). Other TEAEs leading to death were acute myocardial infarction, cholecystitis acute, sepsis, cerebrovascular accident, decubitus ulcer and embolism (one [0.8%] subject each). TEAEs leading to death of sepsis and cerebrovascular accident were considered to be possibly and probably treatment-related, respectively, for one (0.8%) subject each. No other TEAE leading to death was considered to be treatment-related. For the 2 subjects who died during follow-up or more than 30 days after the last dose of study treatment, no AE data were collected; however, the causes of death were recorded as unknown (with no additional information given) and other (thrombosis and cerebral haemorrhage).

In total, 41 (31.5%) subjects reported 86 SAEs during the study. The most frequently reported SAEs were pyrexia (7 [5.4%] subjects), pneumonia (6 [4.6%] subjects), respiratory tract infection (6 [4.6%] subjects), thrombocytopenia (5 [3.8%] subjects) and diarrhoea (5 [3.8%] subjects). No other SAE was reported for more than 2 (1.5%) subjects.

The majority of subjects had at least one TEAE (127 [97.7%] subjects) and at least one treatment-related TEAE (118 [90.8%] subjects). The most frequently reported TEAE was thrombocytopenia (71 [54.6%] subjects), followed by neuropathy (all terms) (52 [40.0%] subjects), anaemia (48 [36.9%] subjects) and diarrhoea (45 [34.6%] subjects).

TEAEs leading to dose withheld were reported for 75 (57.7%) subjects, while only 28 (21.5%) subjects had TEAEs leading to dose reduction.

In total, 27 (20.8%) subjects had TEAEs leading to discontinuation of study treatment, while 17 (13.1%) subjects had treatment-related TEAEs leading to discontinuation of study treatment. The most frequently reported TEAE leading to study treatment discontinuation was neuropathy (all terms) (8 [6.2%] subjects), followed by diarrhoea (4 [3.1%] subjects) and peripheral sensory neuropathy (3 [2.3%] subjects). Seven (5.4%) subjects had NCI Grade 3 treatment-related TEAEs leading to study treatment discontinuation and one (0.8%) subject had NCI Grade 4 treatment-related TEAEs leading to study treatment discontinuation. NCI Grade 3 treatment-related TEAEs leading to study treatment discontinuation of diarrhoea and peripheral sensory neuropathy were each reported for 2 (1.5%) subjects, and multifocal motor neuropathy, neuralgia, neuropathy peripheral and peripheral motor neuropathy were each reported for one (0.8%) subject. NCI Grade 4 treatment-related TEAEs leading to study treatment discontinuation of thrombocytopenia, megacolon and respiratory tract infection were each reported for one (0.8%) subject.

TEAEs of NCI Grades 3 or 4 were reported for 78 (60.0%) subjects: 77 (59.2%) subjects had NCI Grade 3 events and 17 (13.1%) subjects had NCI Grade 4 events. The most frequently reported TEAE and treatment-related TEAE of NCI Grade 3 and 4 severity was thrombocytopenia (NCI Grade 3: 31 [23.8%] subjects and 29 [22.3%] subjects, respectively; NCI Grade 4: 14 [10.8%] subjects and 14 [10.8%] subjects, respectively). The total number of subjects with NCI Grade 3 and 4 TEAEs was similar in Cycles 1 (28 [21.5%] subjects), 2 (33 [26.8%] subjects), 3 (26 [22.6%] subjects) and 6 (18 [21.4%] subjects), and was lower in Cycles 4

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(18 [16.7%] subjects), 5 (16 [17.0%] subjects), 7 (11 [16.4%] subjects) and 8 (6 [10.3%] subjects).

Fifty-three (40.8%) subjects had a total of 111 PN TEAEs during the study. (PN TEAEs were TEAEs contained within the combined term 'neuropathy [all terms]'. Neuropathy [all terms] included multiple individual coded terms across multiple system organ classes.) The most frequently reported individual PN TEAE was peripheral sensory neuropathy (22 [16.9%] subjects), followed by neuropathy peripheral (13 [10.0%] subjects), paraesthesia (12 [9.2%] subjects) and neuralgia (7 [5.4%] subjects). Multifocal motor neuropathy and peripheral motor neuropathy were each reported for one (0.8%) subject. No autonomous neuropathy events were reported.

Among PN TEAEs, no TEAEs of Grade 4 or 5 severity were reported. Within the nervous system disorders system organ class, 11 (8.5%) subjects had at least one Grade 3 PN TEAE. (In addition, 1 [0.8%] subject had at least one Grade 3 PN TEAE included in neuropathy [all terms] within the skin and subcutaneous tissue disorders system organ class [preferred term: skin burning sensation]. Therefore, 12 subjects in total had at least one Grade 3 PN TEAE.) Twenty-five (19.2%) subjects had at least one Grade 2 PN TEAE and 41 (31.5%) subjects had at least one Grade 1 PN TEAE. The most frequently reported individual PN TEAE of NCI Grade 3 severity was peripheral sensory neuropathy (4 [3.1%] subjects), followed by neuropathy peripheral (3 [2.3%] subjects) and neuralgia (2 [1.5%] subjects). No other individual PN TEAE of NCI Grade 3 severity was reported for more than one subject. The most frequently reported individual PN TEAE of NCI Grade 2 severity was also peripheral sensory neuropathy (11 [8.5%] subjects), followed by neuropathy peripheral (5 [3.8%] subjects). Neuralgia and paraesthesia of NCI Grade 2 severity were each reported for 3 (2.3%) subjects, and polyneuropathy of NCI Grade 2 severity was reported for 2 (1.5%) subjects. No other individual PN TEAE of NCI Grade 2 severity was reported for more than one subject. The most frequently reported individual PN TEAE of NCI Grade 1 severity was also peripheral sensory neuropathy (18 [13.8%] subjects), followed by neuropathy peripheral (11 [8.5%] subjects) and paraesthesia (10 [7.7%] subjects). Neuralgia of NCI Grade 1 severity was reported for 4 (3.1%) subjects, and dysaesthesia of NCI Grade 1 severity was reported for 2 (1.5%) subjects. No other individual PN TEAE of NCI Grade 1 severity was reported for more than one subject.

For the purposes of the time to resolution and improvement analyses, PN TEAEs with start and stop dates a day apart were linked into one event; therefore, 73 PN TEAEs were analysed in total: 33 (45.2%) events resolved and 40 (54.8%) events were censored for time to resolution, and 43 (58.9%) events improved and 30 (41.1%) events were censored for time to improvement. The median (range) time to resolution was 8.87 (0.03 to 26.81) months and the median (range) time to improvement was 1.45 (0.03 to 25.69) months. The median time to onset of PN TEAEs was not calculable because the median was not reached; time to onset ranged from 0.13 to 23.52 months. The median (range) follow-up period for the study was 13.3 (3 to 84) months.

Differences were observed in the proportion of subjects who had PN characteristics at baseline between subjects with or without PN TEAEs during the treatment phase and between subjects with starting doses of ≤1.0 or 1.3 mg/m^2 bortezomib; however, none

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of the differences were clinically relevant.
Small mean changes from baseline were observed at the majority of timepoints for all haematology and vital signs parameters.
Physical examination results remained unchanged from screening to the end of treatment visit for the majority of subjects and the majority of body systems.
The most frequently reported subsequent therapy for multiple myeloma was dexamethasone (12 subjects), followed by lenalidomide (9 subjects), thalidomide (5 subjects), cyclophosphamide (4 subjects), bortezomib (Velcade®; 4 subjects), and prednisone (3 subjects).

Conclusion:

- Ten subjects died during the study: 8 [6.2%] subjects had TEAEs leading to death and 2 subjects died during follow-up or more than 30 days after the last dose of study treatment.
- Fifty (39.7%) subjects had a best confirmed response of ≥PR, and 73 (57.9%) subjects had a best confirmed response of ≥MR. Twenty-seven (21.4%) subjects were not evaluable for responses.
- In total, 41 (31.5%) subjects had 86 SAEs during the study. TEAEs of NCI Grades 3 or 4 were reported for 78 (60.0%) subjects: 77 (59.2%) subjects had Grade 3 events and 17 (13.1%) subjects had Grade 4 events. Fifty-three (40.8%) subjects had a total of 111 PN TEAEs during the study. Among PN TEAEs, no TEAEs of Grade 4 or 5 severity were reported. Within the nervous system disorders system organ class, 11 (8.5%) subjects had at least one Grade 3 PN TEAE. (In addition, 1 [0.8%] subject had at least one Grade 3 PN TEAE included in neuropathy [all terms] within the skin and subcutaneous tissue disorders system organ class [preferred term: skin burning sensation]. Therefore, 12 subjects in total had at least one Grade 3 PN TEAE.) Twenty-five (19.2%) subjects had at least one Grade 2 PN TEAE and 41 (31.5%) subjects had at least one Grade 1 PN TEAE. Thirty-three (45.2%) events resolved and 43 (58.9%) events improved. The median (range) time to resolution was 8.87 (0.03 to 26.81) months and the median (range) time to improvement was 1.45 (0.03 to 25.69) months.
- The category with the largest proportion of subjects for serum and urine M-protein best confirmed response was the 100% decrease from baseline category (21 [16.7%] subjects for serum and 18 [14.3%] subjects for urine).
- The median (95% CI) DOR was 6.54 (7.96,7.06) months for subjects with a best confirmed response of ≥PR. The median (95% CI) TTP was 8.38 (7.88,9.56) months. When MR and NC were included, the median (95% CI) TTP was 7.92 (6.73,8.38) months.
- There were no apparent differences between subjects who had a best prior response of CR and those who had a best prior response of PR in the single best response outcomes reported in this study.
- This study shows that retreatment with bortezomib is feasible, provides a good response rate, and does not add new side-effects compared with previous treatment.

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