SYNOPSIS

Issue Date: 24 June 2011

Document No.:EDMS-ERI-26119341:1.0

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development and Millennium Pharmaceuticals, Inc.
Name of Finished Product	VELCADE®
Name of Active Ingredient(s)	bortezomib

Protocol No.: Protocol 26866138-MMY-3002

Title of Study: Final Survival and Subsequent Therapy Update to Clinical Study Report MMY-3002: An Open Label, Randomized Study of VELCADE®-Melphalan-Prednisone Versus Melphalan-Prednisone in Subjects With Previously Untreated Multiple Myeloma

EudraCT Number: 2004-001989-41

Principal Investigator: Jesus San Miguel, M.D. - Hospital Clinico de Salamanca; Salamanca, Spain

Publication (Reference): None for this update report.

Study Period: 30 December 2004 to 24 March 2011 (final cut-off)

Phase of Development: Phase 3

Objectives: The primary objective of this report is to provide the planned, final update on survival and subsequent therapy, based on a clinical cut-off date of 24 March 2011, for subjects enrolled in Study MMY-3002. In addition, an ad hoc analysis was performed to determine the incidence of second primary malignancies.

Methodology: Subjects in Study MMY-3002 were randomly assigned to 1 of 2 treatment groups (Vc-MP or MP) and were stratified according to baseline $beta_2$-microglobulin, baseline albumin levels, and region. Subjects in the Vc-MP treatment group received VELCADE 1.3 mg/m^2 twice-weekly for four 6-week cycles, followed by weekly dosing on Days 1, 8, 22, and 29 for five 6-week cycles, in combination with melphalan 9 mg/m^2 and prednisone 60 mg/m^2 once daily on Days 1 to 4 of each 6-week cycle. Subjects in the MP treatment group received 9 cycles of melphalan 9 mg/m^2 and prednisone 60 mg/m^2 once daily on Days 1 to 4 of each 6–week cycle. For both groups, treatment continued for a maximum of 9 cycles (54 weeks). Following the completion of study treatment, follow-up for survival and time to subsequent therapy continued until 4.5 years after the last subject was randomized to the study. The detailed study design was presented in the initial 2007 CSR for Study MMY-3002.

Collection of Data for Second Primary Malignancies (SPMs):

Since December 2010, there have been emerging reports that new treatments for multiple myeloma, in particular immunomodulating agents like lenalidomide, might be associated with an increase risk of SPMs, especially hematologic malignancies such as acute myeloid leukemia, B-cell lymphoma, and myelodysplastic syndromes. As a result, the sponsor retrospectively collected reports of SPMs. Events of interest included both hematologic and non-hematologic neoplasms. Collection of these data commenced in February 2011 and concluded in March 2011, and the SPM data are summarized in this synopsis.

Statistical Methods:

Statistical Hypothesis Objective: Since Study MMY-3002 reached a definitive conclusion at the third planned interim analysis and the first update in 2008 provided further supportive evidence of a survival benefit, followed by a more precise characterization of long-term survival data in the second update, the main purpose of this update is to provide a final report on the long-term survival of subjects who participated in Study MMY-3002. In addition, assessments of subsequent therapy and best response to subsequent therapy are included in this update. Unadjusted p-values are provided for comparisons between the 2 treatment groups.

Efficacy Analysis Specifications

The efficacy variables analyzed were OS and time to subsequent therapy. In addition, subsequent therapy and best response to subsequent therapy were also tabulated and are presented as part of the analysis results.

Safety Analysis Specifications

The ad hoc data on the incidence of SPMs were analyzed by the following methods. Previous analyses of this study had demonstrated that the addition of VELCADE to the MP regimen led to prolonged OS, which hypothetically could lead to an increased probability of detecting secondary malignancies due to expected longer follow-up for SPMs in the Vc-MP treatment group. For this reason, 2 types of incidence rates were calculated for the safety population: incidence proportions, defined as the percentage of the subjects reporting any SPM in the safety population with available information; and incidence rates, defined by the number of the subjects reporting any SPM divided by the total duration of follow-up (patient-years=pt-yrs) in the safety population with available information up to the onset of SPMs. For incidence proportions, the relative risks, defined as the ratio of incidence proportions between the 2 randomized treatment groups, were provided along with their 95% confidence intervals (CIs). For incidence rates, the relative risks, along with their 95% CIs, were calculated using an exponential regression model for lifetime data (assuming constant hazards). Due to the distinct nature of hematologic and non-hematologic neoplasms, as well as the emerging signals of SPM for immunomodulating agents, analyses of SPMs were performed separately for hematologic and non-hematologic SPMs (all SPMs and those with fatal outcomes).

Results:

STUDY POPULATION: As of the clinical cut-off (end of study) of 24 March 2011 for this planned final analysis, a total of 682 subjects from 151 centers in 22 countries were randomized into Study MMY-3002, with 344 subjects randomized to the Vc-MP treatment group and 338 subjects randomized to the MP treatment group. These subjects are described in detail in Section 4.1 of the initial 2007 CSR for Study MMY-3002 CSR. Updated survival data, the time to subsequent therapy, the response to subsequent therapy, and the incidence of second primary malignancy for these subjects are presented in this final report. Subject disposition: The protocol-defined end of the study, specified to occur 4.5 years after last subject randomized, was reached on 24 March 2011. At this time, 228 (33%) (Vc-MP: 39% vs. MP: 28%) randomized subjects were still in long-term follow-up, while 387 subjects (57%) (Vc-MP: 51% vs. MP: 62%) had died. In addition, 5% of subjects in both groups were lost to follow-up and 4% of subjects in both treatment groups chose to withdraw from the study. The median duration of follow-up was 60.1 months for the entire ITT population and was similar between the treatment groups (Vc-MP: 59.9 months vs. MP: 60.3 months)

EFFICACY RESULTS:

Overall Survival: At the time of clinical cut-off (24 March 2011) for this final survival update, 387 randomized subjects had died (176 subjects [51.2%] in the Vc-MP treatment group, and 211 subjects [62.4%] in the MP treatment group). There was a 30.5% reduction in the risk of death in the Vc-MP treatment group as compared with the MP treatment group. The HR for OS (Vc-MP vs. MP treatment group) was 0.695 (95% CI: 0.567, 0.852) and the unadjusted p-value was 0.00043 (stratified log-rank test). The median OS was 56.4 months in the Vc-MP treatment group and 43.1 months in the MP treatment group. The 5-year survival rate was 46.0% (95% CI: 40.3; 51.8) in the Vc-MP group and 34.4% (95% CI: 28.9%; 39.9%) in the MP treatment group. It should be noted that the median OS benefit of 13.3 months for the Vc-MP treatment group was obtained despite the use of a VELCADE-containing regimen in 59% of subjects in the MP treatment group who later received subsequent therapy. With a median follow-up of 5 years, these updated OS data demonstrated the substantial, long-lasting survival benefit for the Vc-MP treatment compared with treatment with MP alone. This survival benefit was previously reported in the initial 2007 CSR for Study MMY-3002 (HR: 0.607), the 2008 update to the CSR (HR: 0.644), and the 2009 OS update to the CSR (HR: 0.653), and continues, as reported in this final OS update (HR of 0.695 [95% CI: 0.567, 0.852]). Overall survival relative to baseline stratification factors ($beta_2$-microglobulin, albumin, region), demographic data (sex, race, and age), and disease characteristics (International Staging System staging [ISS] and cytogenetic abnormalities) was evaluated as pre-planned. The hazard ratios for most subgroups were consistently <1 with the exception of 2 subgroups (North American subjects and subjects with a high risk cytogenetic profile), demonstrating a survival benefit for subjects in the Vc-MP treatment group for most of the subgroups. It should be noted that there are small numbers of subjects in these 2 subgroups. Overall, the findings are consistent with previous analyses performed.

Overall Survival: Analyses Over Time

Table 1 presents the OS of the treatment groups at each critical cut-off date. The Vc-MP group consistently showed a significant and substantial OS benefit compared with the MP group. At the final analysis, a median OS of 56.4 months, represented an improvement of more than 1 year (13.3 months) compared with the MP group (median OS = 43.1 months), despite the fact that 59% (145/246) of the retreated MP subjects received VELCADE-containing regimens after the study treatment.

Table 1: Overall Survival: Analyses Over Time

Date	Death (n)	MP Median OS	Vc-MP Median OS	Hazard Ratio (95% CI)	P value
Initial (2007)	121	Not Reached	Not Reached	0.607 (0.419; 0.880)	0.00782
Update 1 (2008)	186	Not Reached	Not Reached	0.644 (0.480; 0.865)	0.003215
Update 2 (2009)	257	43.1 months	Not Reached	0.653 (0.508; 0.840)	0.000835
Final (2011)	387	43.1 months	56.4 months	0.695 (0.567; 0.852)	0.000427

MP=melphalan-prednisone; Vc-MP=VELCADE-melphalan-prednisone; OS=overall survival; CI=confidence interval

SAFETY RESULTS: No new safety update was planned for this final OS update to the CSR for Study MMY 3002. In view of the emerging reports that new treatments for multiple myeloma, in particular immunomodulatory drugs, like lenalidomide, appear to be associated with a higher risk for developing a SPM, the sponsor decided to perform an unplanned ad hoc exploratory analysis of these events on Study MMY-3002. Events of interest included both hematologic and non-hematologic neoplasms. Despite the unplanned nature of the analysis, data were collected for 96% of the subjects. The background incidence of malignancy in patients 65-74 years of age was 1.9 incidences/100 pt-yr and in patients 75-84 years of age was 2.4 incidences/100 pt-yr (SEER database).

The incidence rate of hematologic malignancies, as reported by the investigator, was low in both treatment groups, and no difference was observed between the 2 groups (Vc-MP: 1%, MP: 1%). It should be noted that all 3 subjects in the MP treatment group who developed hematologic malignancies developed them before any subsequent therapy was received. Hence, the comparison was not confounded by subsequent treatments. With a median follow-up of 5 years (60.1 months), no difference was observed in hematologic malignancies with fatal outcome. There was no difference in the incidence rate per 100 pt-yr between the treatment groups (Vc-MP: 0.26/100 pt-yr vs. MP: 0.30/100 pt-yr) and these incidence rates are lower than the background incidence rate in the patient age population (1.9/100 pt-yr for 65-74 years of age and 2.4/100 pt-yr for 75-84 years of age).

The incidence rate of non-hematologic malignancies, as reported by the investigator, was low in both groups (Vc-MP: 5%; MP: 3%). Detection of SPMs may be slightly increased in the Vc-MP group due to the extended OS (increase of 13.3 months in median OS). In addition, no difference was observed in non-hematologic malignancies with fatal outcome (Vc-MP: 2% vs MP: 2%). There was no difference in the incidence rate per 100 patient years between treatment groups (Vc-MP: 1.40/100 pt-yr vs. MP: 1.00/100 pt-yr) and these incidence rates were slightly lower compared with the background incidence rate in the patient age population (1.9 and 2.4/100 pt-yr for 65-74 years and 75-84 years, respectively).

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION(S): These final analyses confirm the robustness of the clinical benefit of the Vc-MP regimen, and show extended survival benefit in the Vc-MP treatment group (HR: 0.695; p=0.00043). With a median follow-up of 5 years (60.1 months), the median survival was 56.4 months in the Vc-MP treatment group and 43.1 months in the MP treatment group and, representing a 30.5% reduction in the risk of death for subjects treated with the Vc-MP combination. Importantly, the OS benefit observed in the Vc-MP treatment group was observed despite the use of VELCADE or VELCADE-containing regimens in 59% of the subjects in the MP treatment group who received subsequent therapy. A retrospective collection of incidence data for SPMs showed no evidence for any increased risk of SPM associated with VELCADE treatment.

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