1 Study Synopsis

Name of Sponsor/Company:	Janssen-Cilag International NV
Name of IMP:	Velcade®
Name of Active Ingredient:	Bortezomib
Protocol Number:	26866138MMY2038
Title of Study: A Phase 2, Multicentre, Randomised, Open-Label, Parallel Group Study to Evaluate the Safety and Efficacy of Velcade® when added to Adriamycin-Dexamethasone Treatment versus Vincristine-Adriamycin-Dexamethasone Standard Treatment in Subjects with Multiple Myeloma who are Refractory to or Have Relapsed after Primary Therapy for Multiple Myeloma.	
EudraCT Number: 2006-001709-27	
Co-ordinating Investigator: Prof. Wolfgang Knauf, MD, Onkologische Gemeinschaftspraxis, Frankfurt, Germany.	
Study Centres: 12 sites: 2 in Germany, 1 in Hungary, 3 in Lithuania, 3 in Poland and 3 in Russia.	
Publication (Reference): None	
Studied Period: 05 Dec 2006 to 28 Feb 2008	**Phase of Development:** Phase II
Objectives: The primary objective originally was to assess the safety and efficacy of replacing vincristine with Velcade® (bortezomib, also named PS341) in the standard therapy vincristine, adriamycin and dexamethasone (VAD) in subjects with multiple myeloma who were refractory to or had relapsed after their primary therapy for multiple myeloma. The efficacy response was to be measured by the response rate (RR) of the disease. However, following a substantial decline in the use of the VAD regimen as a standard of care in treatment of second line multiple myeloma, the required number of study subjects could not be recruited in a reasonable time period. As a result, recruitment of the study was halted at 30 study subjects. Because of the low subject numbers, there was insufficient power to detect any statistically significant difference between the treatment groups, for the planned efficacy analysis. The secondary objectives originally were to assess the duration of response, event free survival, the time to progression, the one year survival and the overall survival of the subjects treated with Velcade® in combination with adriamycin and dexamethasone (PAD therapy) *vs* VAD standard therapy. However, the follow-up of the subject's treatment was limited to follow-up for safety as per the protocol. It was not possible to statistically evaluate any long-term efficacy parameter.	
Methodology: This was an international, multicentre, randomised, open label, parallel group Phase II study in subjects with multiple myeloma who were refractory to or had relapsed after their primary therapy for multiple myeloma. After providing written informed consent, subjects were evaluated for eligibility during a 14 day screening period. Subjects were considered for eligibility when the investigator would treat the subject with a combination therapy of VAD standard therapy. Baseline efficacy and safety assessments were performed on Day 1 prior to administration of study drug. After screening, a central randomisation (using the interactive voice response system) to treatment with PAD *vs* VAD took place at baseline (1:1). The randomisation was stratified by primary therapy, age (65 years or more *vs* less than 65 years), and country. After randomisation, subjects received therapy for up to 8 treatment cycles. Each cycle	

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consisted of 4 weeks of treatment. Treatment beyond 6 cycles was to be discussed on a case-by-case basis. Optimally, subjects who had a confirmed complete response (CR), as specified by the European Group for Blood and Marrow Transplantation (EBMT) criteria and acceptable tolerability, were to receive 2 additional treatment cycles. Subjects who had disease progression before completing 2 treatment cycles could, at the investigator's discretion, continue in the study until at least 2 full treatment cycles were completed. After the treatment period, subjects were followed up for safety only.	
Number of Subjects (Planned and Analysed): In the original protocol, approximately 212 subjects were planned to be recruited to this study. Following Protocol Amendment INT-2 (09 Jul 2007), approximately 30 subjects were to be recruited. Thirty-one subjects were screened, 30 subjects were randomised and 29 subjects were treated during the study. Twenty-nine subjects (16 subjects in the VAD group and 13 subjects in the PAD group) were included in the safety population and 28 subjects (15 subjects in the VAD group and 13 subjects in the PAD group) were included in the intention to treat population.	
Diagnosis and Main Criteria for Inclusion: Male or female subjects aged ≥18 years with multiple myeloma who were refractory to or had relapsed after their primary therapy for multiple myeloma and would have been treated with a combination therapy of VAD. Subjects had to have a Karnofsky performance status (KPS) of ≥60 and an estimated life expectancy of at least 6 months at Screening.	
Test Product, Dose and Mode of Administration, Batch Number: Velcade® (1.3 mg/m^2 IV bolus administered on Days 1, 4, 8 and 11 of each cycle, Batch Numbers V06P E9685, V06P F9729, V06P J9833 and V07PD7021), in combination with adriamycin (9 mg/m^2 IV push administered on Days 1 to 4 of each cycle, commercial source used, no batch number available) and dexamethasone (40 mg oral dose administered on Days 1 to 4, 9 to 12 and 17 to 20 of the first cycle and on Days 1 to 4 and 17 to 20 of all subsequent cycles, commercial source used, no batch number available).	
Duration of Treatment: Subjects could be treated for a maximum of 8 cycles, each consisting of 4 weeks of treatment. Subjects were followed up monthly until disease progression or relapse. Thereafter follow-up was performed every other month.	
Reference Therapy, Dose and Mode of Administration, Batch Number: VAD treatment comprised vincristine (0.4 mg IV push administered on Days 1 to 4 of each cycle, commercial source used, no batch number available), adriamycin (9 mg/m^2 IV push administered on Days 1 to 4 of each cycle, commercial source used, no batch number available) and dexamethasone (40 mg oral dose administered on Days 1 to 4, 9 to 12 and 17 to 20 of the first cycle and on Days 1 to 4 and 17 to 20 of all subsequent cycles, commercial source used, no batch number available).	
Criteria for Evaluation:	
Efficacy: Response to therapy was assessed according to the EBMT criteria and was based on relative changes in serum and urine monoclonal protein (M-protein) concentrations. KPS was also assessed. Skeletal X-rays were to be performed, if required.	

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Safety: Safety was assessed by the monitoring of adverse events (AEs), physical examination (including neurological/peripheral neurological examination), vital signs measurements (heart rate, respiratory rate, temperature, and supine and standing systolic and diastolic pressure), weight, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and completion of the Functional Assessment of Cancer Therapy/Gynaenocologic Oncology Group Neurotoxicity (FACT/GOG-Ntx) questionnaire.

Statistical Methods: Due to the low subject numbers, there was insufficient power to detect any statistically significant difference between the treatment groups. Therefore, no statistical analyses were performed. Summary statistics were presented, where appropriate.

Summary – Conclusions:

Efficacy Results: The primary efficacy endpoint was Response Rate as defined by the combination of subjects with CR and partial response (PR) according to the EBMT criteria. There was a higher response rate in the PAD group than in the VAD group (33.3% in the VAD group and 53.8% in the PAD group). There was no difference in the response rate (CR + PR + MR) between the VAD group (46.7%) and the PAD group (53.8%). There were lower percentages of subjects with minimal response and no change in the PAD group in comparison with the VAD group. There was no difference between treatment groups in the percentage of subjects with PD.

There was insufficient data to perform the Kaplan-Meier analysis planned to evaluate the secondary efficacy endpoint of duration of response.

A higher percentage of subjects in the PAD group (54%) had a serum M-protein best confirmed response of ≥50% compared with subjects in the VAD group (27%). An equal number of subjects in each treatment group had urine M-protein best confirmed response of ≥90% to ≤100%. However, there was a high percentage of subjects with missing data in both treatment groups for both serum and urine M-protein. This was as a result of either the test not being done, the test not being applicable, the results not being confirmed (2 results at least 6 weeks apart), or the subject was no longer in the study. There were no median changes from baseline to the final or last value in either treatment group with regard to KPS score.

Safety Results: Eleven subjects reported serious adverse events (SAEs) during the study, and of these, 3 subjects died. In the VAD group, 6 (37.5%) subjects reported SAEs, of whom 3 (18.8%) subjects died. In the PAD group, no subject died and 5 (38.5%) subjects reported SAEs. In the VAD group, the most frequently reported SAE was pneumonia (2 subjects). No other SAE was reported for more than one subject in the VAD group or the PAD group.

A greater percentage of subjects in the VAD group reported treatment-emergent adverse events (TEAEs) and drug–related TEAEs in comparison with the PAD group. In the VAD treatment group, the most frequently reported TEAEs were neutropenia, lymphopenia, fatigue and acute bronchitis and the most frequently reported drug-related TEAEs were neutropenia and lymphopenia. In the PAD group, the most frequently reported TEAE was insomnia and the most frequently reported drug-related TEAEs were diarrhoea, asthenia, peripheral sensory neuropathy, insomnia and hypertension.

A greater percentage of subjects in the VAD group reported TEAEs leading to

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discontinuation of study drug compared with subjects in the PAD group. In the VAD group, the following TEAEs were each reported in one subject, leading to discontinuation of study drug: neutropenia, death, sudden cardiac death, pneumonia, septic shock and cerebrovascular accident. In the PAD group, the following TEAEs were each reported in one subject, leading to discontinuation of study drug: unstable angina, chronic cardiac failure and pyelonephritis.

One subject in the VAD group and 3 subjects in the PAD group reported events of peripheral neuropathy.

In the VAD group, there were median changes from baseline in white blood cell (WBC) count, neutrophil, lymphocyte, monocyte and eosinophil levels for haematology variables and in alkaline phosphatase (ALP) and C-reative protein (CRP) for clinical chemistry variables during the study. In the PAD group, there were median changes from baseline in WBC count, neutrophil, lymphocyte, monocyte, eosinophil, platelet and basophil levels for haematology variables and in ALP, lactose dehydrogenase and CRP for clinical chemistry variables during the study. Eight (50%) subjects in the VAD group and 3 (23.1%) subjects in the PAD group had a laboratory abnormality reported as an AE. One (6.3%) subject in the VAD group and 2 (15.4%) subjects in the PAD group had a clinical chemistry abnormality reported as an AE. There were no other notable changes from baseline or differences between treatment groups with regard to haematology or clinical chemistry results. There were no notable mean changes from baseline in any vital signs variable, body weight or BSA for either treatment group. A change from Screening in physical examination findings was reported for an equal number of subjects in each treatment group.

Conclusion: The objectives of the study could not be addressed because the number of subjects was low and there was insufficient power to detect any statistically significant difference between the treatment groups after the study was terminated prematurely.