SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development and Millennium Pharmaceuticals, Inc.
Name of Finished Product	VELCADE® for Injection
Name of Active Ingredient(s)	bortezomib (JNJ-26866138)

Protocol No.: 26866138-LUC-2001

Title of Study: A Randomized, Open-Label, Multicenter Study of Alimta® (pemetrexed) Plus VELCADE® (bortezomib) or Alimta Alone or VELCADE Alone in Subjects With Locally Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Failed Prior Antineoplastic Therapy

Principal Investigator: Giorgio V. Scagliotti, M.D. – University of Torino, Department of Clinical and Biological Sciences, Thoracic Oncology Unit, San Luigi Hospital-Regione Gonzale 10, 10043 Orbassano, Torino, Italy

Publication (Reference): None

Study Period: 16 February 2006 to 19 October 2007; date of database lock = 19 December 2007

Phase of Development: 2

Objectives: The primary objective of this study was to establish the objective response rate (complete response [CR] + partial response [PR]) following treatment with Alimta plus VELCADE, Alimta alone, or VELCADE alone in subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) who had failed prior chemotherapy for Stage IIIb/IV NSCLC. The Alimta alone treatment group was used as the control. The VELCADE single-agent treatment group was used to determine if VELCADE administered weekly could demonstrate response rates. Results of this study were to be used for future decision-making and design of a confirmatory Phase 3 study.

Secondary objectives of this study included assessment of the following in all treatment groups:

- Disease control rates including CR, PR, and stable disease (SD)
- Time to tumor progression (TTP), time to response, duration of response, and duration of disease control
- Progression-free survival (PFS), overall survival (OS), and 6- and 12-month survival rates
- Evaluation of safety throughout the study

Exploratory objectives for this study sought to identify subject populations that were more or less likely to respond to VELCADE or Alimta plus VELCADE or Alimta alone through the evaluation of a defined set of pharmacogenomic markers and biomarkers.

Methods: This was a randomized, open-label, multicenter study consisting of 3 phases: a prerandomization (screening) phase, an open-label treatment phase, and a posttreatment phase. Subjects with locally advanced or metastatic NSCLC who had failed prior systemic chemotherapy for Stage IIIb/IV NSCLC were eligible for enrollment in this study (1 additional prior line was allowed if given as neoadjuvant or adjuvant therapy). Subjects were randomly assigned to 1 of 3 treatment groups: Group A (Alimta + VELCADE), Group B (Alimta), and Group C (VELCADE). Stratification was based on time since last chemotherapy (<3 months or ≥3 months), histology type (adenocarcinoma or others), and geographic region (European countries or others). The randomization was implemented through a centralized Interactive Voice Response System (IVRS). Study eligibility was determined during the screening phase, and baseline evaluations were performed within 14 days before randomization. An Independent Review Committee was constituted to review the efficacy and

preliminary safety data. An Independent Radiology Board was constituted to review the efficacy assessments at the time of the interim analysis (focusing on responders only) and at the end of the study.

Number of Subjects (planned and analyzed): The planned sample size was approximately 135 subjects, with at least 120 subjects (40 per treatment group) evaluable in the final analysis. A total of 155 subjects were enrolled and randomized: 52 to Group A, 51 to Group B, and 52 to Group C. The intent-to-treat population equals the safety population (all subjects who received at least 1 dose of VELCADE or Alimta). The response-evaluable includes all subjects who had no major protocol deviation, who had received at least 1 dose of study drug, and who had at least 1 response assessment after baseline (unless objective progressive disease [PD] was determined). The response-evaluable population comprised 130 subjects: 45 in Group A, 45 in Group B, and 40 in Group C.

Diagnosis and Main Criteria for Inclusion: Subjects must have satisfied the following criteria to be enrolled in this study:

- Men or women, 18 years of age or older
- Histological or cytological confirmation of NSCLC
- Subject had relapsed or refractory locally advanced (Stage IIIb) or metastatic (Stage IV) NSCLC
- Failure of 1 prior line of systemic chemotherapy for Stage IIIb/IV NSCLC (1 additional prior line allowed if given as neoadjuvant or adjuvant therapy to tumor resection
- Documentation of PD since previous systemic chemotherapy
- Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) criteria
- ECOG performance status score of 0 or 1

Test Product, Dose and Mode of Administration, Batch No.: VELCADE was administered as a 3-second intravenous (i.v.) bolus on Days 1 and 8. For subjects in Group A, VELCADE was administered 60 minutes after the end of the Alimta infusion. The starting dose of VELCADE in this study was 1.6 mg/m^2. Protocol-specified dose modifications were made as necessary. Two dose reductions were allowed (1.6 to 1.3 to 1.0 mg/m^2). Doses could be held or reduced based on the severity of and the recovery from a previous toxicity. Dose escalations or re-escalations were not allowed. Batch numbers for VELCADE were D05PJ7454, D05PH7448, D06PE7501, D06PC7489.

Reference Therapy, Dose and Mode of Administration, Batch No.: Alimta was administered as a 10-minute i.v. infusion on Day 1 of each cycle. Alimta was administered at the standard registered dose (500 mg/m^2) for patients with NSCLC. Premedication with dexamethasone, folic acid, and vitamin B_{12} was mandatory to reduce the severity and frequency of hematologic and nonhematologic toxicity of Alimta. Protocol-specified dose modifications were made as necessary. Two dose reductions were allowed (500 to 400 to 300 mg/m^2). Doses could be held or reduced based on the severity of and the recovery from a previous toxicity. Dose escalations or re-escalations were not allowed. Batch numbers for Alimta were D06PA7469, V07PC7005, D06PC7491.

Duration of Treatment: For all treatment groups, therapy cycles were repeated until PD, unacceptable toxicity, or any other criterion for withdrawal for treatment was met. In the case of CR, treatment was to continue for at least 2 cycles beyond the date of confirmation of CR.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the objective response rate. Secondary efficacy endpoints included disease control rate, TTP, PFS, survival (6-month, 12-month, and OS), time to response, duration of response, and duration of disease control. Throughout the open-label treatment phase (and posttreatment phase, in case the subject did not reach PD at the time of discontinuation of therapy), the investigator assessed the subject's response to therapy using the results of efficacy evaluations conducted at equivalent frequencies in each treatment group according to the RECIST guidelines. Subjects with confirmed CR were followed for PD and survival. During the posttreatment phase, all

subjects were followed every 3 months for assessment of survival. Subjects who discontinued treatment without PD had disease assessments every 6 weeks until documentation of PD. However, subjects with an unconfirmed response were to return at least 4 weeks after the discontinuation of treatment for an additional disease assessment to confirm the subject's response to therapy.

Pharmacogenomics: Pharmacogenomic and biomarker testing were applicable only for those countries where the health authorities and ethics committees approved this testing. Subjects were required to sign a separate informed consent form indicating their willingness to participate in the mandatory pharmacogenomic and biomarker analyses and the optional future testing.

Safety: Safety was evaluated throughout the study by assessment of adverse events, clinically significant changes in physical examinations, 11-item Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) scores, Eastern Cooperative Oncology Group (ECOG) performance scores, vital signs, and clinical laboratory findings. The severity of adverse events was scored using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. Summary statistics were provided for safety parameters. Exposure to investigational product and reasons for discontinuation of study treatment were tabulated as well.

Statistical Methods:

Sample size: The sample size calculation was based on the assumption that approximately 135 subjects would be needed to ensure that at least 120 subjects (40 per treatment group) would be evaluable in the final analysis. Based on the approach of Simon's randomized Phase 2 design, this total sample size provided a 89.7% probability to observe a better objective response rate in Group A than in Group B if the underlying response rates were 20% (Group A) and 9% (Group B), respectively.

Analyses: An estimate of the response rate in each treatment group was presented with exact 2-sided 95% confidence intervals. The number and percentage of subjects included in each category was descriptively tabulated. The response rates between treatment groups were compared using the stratified Cochran-Mantel-Haenszel test. TTP, PFS, and OS between treatments were compared using stratified log-rank tests. Analyses of these time-to-event endpoints focused on the intent-to-treat population. The Kaplan-Meier method was used to estimate the distribution of these endpoints for each treatment group. Six-month and 12-month survival rates also were estimated by the Kaplan-Meier method. Cox regression including stratification variables and other prognostic factors also was used to obtain hazard-ratio estimates and confidence intervals. Time to response, duration of response, and duration of disease control were summarized descriptively. Summary statistics were provided for safety parameters. Three interim analyses of efficacy and one interim analysis of safety were performed for this study.

RESULTS: The most common reason for discontinuation of study treatment was disease progression.

Study Withdrawal Information
(Study 26866138-LUC-2001: All Randomized Subjects Analysis Set)

	Alimta + VELCADE (N=52) n (%)	Alimta Alone (N=51) n (%)	VELCADE Alone (N=52) n (%)	Total (N=155) n (%)
Disease progression	34 (65)	31 (61)	40 (77)	105 (68)
Adverse event	5 (10)	7 (14)	2 (4)	14 (9)
Death	2 (4)	1 (2)	5 (10)	8 (5)
Subject choice (subject withdrew consent)	3 (6)	2 (4)	1 (2)	6 (4)
Loss to follow-up	1 (2)	0	0	1 (1)
Sponsor decision	0	1 (2)	0	1 (1)
Other	7 (13)	9 (18)	4 (8)	20 (13)

The mean age was 59.5 years. Most (97%) of the population was white, and 72% of subjects were men. Most subjects (80%) had an ECOG performance status score of 1. Baseline demographics and disease characteristics were generally similar among the 3 treatment groups. The demographic and baseline characteristics for the response-evaluable analysis set were generally similar to those of the intent-to-treat analysis set, except that there were slightly more females in the VELCADE + Alimta group (18/52, 35%) than in the Alimta (15/51, 29%) and VELCADE alone (11/52, 21%) groups.

EFFICACY RESULTS: The efficacy results for the intent-to-treat population are summarized in this synopsis. In general, the efficacy results for the response-evaluable population were similar to those of the intent-to-treat population. The three interim analyses provided efficacy results that are consistent with those in the final analysis.

Primary Efficacy Analysis: No response or survival advantage was seen with Alimta and VELCADE in combination compared with either drug alone. The response rate was 6% in Group A, 4% in Group B, and 0% in Group C. The disease control rate (CR+PR+SD) was 65% in Group A, 59% in Group B, and 33% in Group C. Assessment of best overall response by independent radiology review did not show improvement compared to investigator assessments, but did demonstrate a similar trend between study arms. Likewise, assessment by algorithm showed similar trends.

Secondary Efficacy Analyses:

- The median TTP was 122 days (95% confidence interval [CI]: 79, 136) for subjects in Group A, 89 (45, 136) days for subjects in Group B, and 43 (41, 70) days for subjects in Group C.
- The median time to response in Group A was 215 days (range = 42 – 215 days). In Group B, the time to response was 37 days for 1 responder and 474 days for the other responder.
- The median duration of response in Group A was 267 days (95% CI: 122, 267). In Group B, the duration of response was 86 days for 1 responder and 422+ days for the other responder.
- The median duration of disease control was 150 days (95% CI: 124, 184) in Group A, 170 (126, 265) days in Group B, and 92 (80, 150) days in Group C.
- Median PFS was 110 days (95% CI: 77, 136) for subjects in Group A, 86 (45, 136) days for subjects in Group B, and 45 (41, 70) days for subjects in Group C.
- Median OS was 261 days (95% CI: 188, 355) for subjects in Group A, 388 (251, 474) days for subjects in Group B, and 237 (149, 310) days for subjects in Group C. The 6-month survival rate was 66.7% for subjects in Group A, 76.5% for subjects in Group B, and 59.0% for subjects in Group C. The 12-month survival rate was 35.9% for subjects in Group A, 52.5% for subjects in Group B, and 31.5% for subjects in Group C.
- Assessment of the secondary efficacy variables by independent radiology review and assessment by algorithm generally were similar to those of the investigator assessment.
- The post-study chemotherapies were generally comparable amongst the 3 treatment groups.

PHARMACOGENOMIC RESULTS: Tumor samples were collected for 80 individuals in this study.

Mutations in the *KRAS*, *EGFR*, and *TP53* genes were examined in DNA isolated from somatic tissue samples. Germline polymorphisms in the *PSMB1* and *PSMB5* genes were examined in DNA isolated from peripheral blood samples. The alleles and mutations analyzed and detected can be found in Appendix 1.3. Statistical analysis of these data in relation to study endpoints will be reported separately.

The analyses of germline polymorphisms in the *GARFT*, *DHFR*, *TS*, and *CYP2C19* genes in DNA isolated from peripheral blood samples were not performed as planned due to mechanistic relevance to Alimta (*GARFT*, *DHFR*, *TS*) and lack of response data (*CYP2CI9*). The analyses of mutations in the *PSMB* genes in DNA isolated from somatic tissue samples were not performed as planned due to limited availability of tumor sample.

Additional known biomarkers relevant to molecular targets of the proteasome, of apoptosis, of cell-cycle progression, of angiogenesis, and of NSCLC prognosis (such as p53, cyclin D1, Ki-67, $p21^{cip1}$, $p27^{kip1}$, and TTF-1) were planned for analyses; however, analyses were not conducted due to the limited number of responders in this study.

SAFETY RESULTS: One interim analysis of safety was performed for this study. No major safety concerns were observed.

The table below provides an overview of the various categories of adverse events.

Overview of Adverse Events
(Study 26866138-LUC-2001: Safety Analysis Set)

Subjects with:	Alimta + VELCADE (N=52)	Alimta Alone (N=51)	VELCADE Alone (N=52)	Total (N=155)
Adverse events	**49 (94)**	**48 (94)**	**47 (90)**	**144 (93)**
Drug-related adverse events	43 (83)	40 (78)	27 (52)	110 (71)
Grade 3, 4, or 5 adverse events	**29 (56)**	**21 (41)**	**23 (44)**	**73 (47)**
Maximum Grade 3	12 (23)	15 (29)	14 (27)	41 (26)
Maximum Grade 4	11 (21)	4 (8)	3 (6)	18 (12)
Maximum Grade 5	6 (12)	2 (4)	6 (12)	14 (9)
Drug-related Grade 3, 4, or 5 adverse events	25 (48)	17 (33)	7 (13)	49 (32)
Serious adverse events	**19 (37)**	**12 (24)**	**16 (31)**	**47 (30)**
Drug-related serious adverse events	15 (29)	7 (14)	2 (4)	24 (15)
Adverse events leading to treatment termination	**10 (19)**	**7 (14)**	**5 (10)**	**22 (14)**
VELCADE-related adverse events leading to treatment discontinuation	6 (12)	0	1 (2)	7 (5)
Alimta-related adverse events leading to treatment discontinuation	5 (10)	7 (14)	0	12 (8)
Deaths due to an adverse event[a]	**6 (12)**	**2 (4)**	**6 (12)**	**14 (9)**
Drug-related adverse events resulting in death[a]	6 (12)	2 (4)	6 (12)	14 (9)

Group A: Alimta 500 mg/m^2 on Day 1 of a 21-day treatment cycle with VELCADE 1.6 mg/m^2 on Days 1 and 8.
Group B: Alimta 500 mg/m^2 on Day 1 of a 21-day treatment cycle.
Group C: VELCADE 1.6 mg/m^2 on Days 1 and 8 of a 21-day treatment cycle.
[a] All deaths, including during the study and after the study.
Key: Related = possibly, probably, or very likely related to the study drug.

Adverse Events: The adverse event profile reflects those of single agents. In total, 93% of subjects reported adverse events. The most frequently reported (>20% of subjects) adverse events in Group A were thrombocytopenia (31%), dyspnea (27%), fatigue (27%), nausea (25%), asthenia (21%), and neutropenia (21%). In Group B, the most common adverse events were nausea (35%), asthenia (27%), and fatigue (22%). In Group C, the most common adverse events were fatigue (25%), dyspnea (23%), and anorexia (21%).

Grade 3, 4, or 5 adverse events were reported in 56% of subjects in Group A, 41% of subjects in Group B, and 44% of subjects in Group C. The most commonly reported (at least 5% of subjects) Grade 3, 4, or 5 adverse events were neutropenia (10%), dyspnea (9%), thrombocytopenia (8%), and fatigue (5%). The incidence of Grade 4 adverse events was higher in Group A (21%) than in Group B (8%) or Group C (6%)

Drug-related adverse events were reported in 83% of subjects in Group A, 78% in Group B, and 52% in Group C. Nausea and fatigue were among the most frequently reported drug-related adverse events in each treatment group. The incidence of drug-related Grade 3, 4, or 5 adverse events was higher in subjects in Group A (48%) and in Group B (33%) than in Group C (13%). The most commonly

reported (at least 5% of subjects) drug-related Grade 3, 4, or 5 adverse events were neutropenia (10%) and thrombocytopenia (8%).

Deaths: A total of 113 subjects (73%) died during the study. Most (101/113, 89%) deaths were due to progressive disease. The cause of death for those reported within 30 days of the first dose of study treatment, within 60 days of the first dose, and within 30 days of the last dose have been reviewed. Taken together with the small number of deaths reported, the clinical relevance of the higher percentage of deaths in the Group C compared to the other 2 groups is unclear. For 5 subjects (3%), the main cause of death during the study was an adverse event: pancytopenia, circulatory collapse, bronchopneumonia, appendiceal abscess, and respiratory failure. For 4 of these subjects, the adverse event leading to death was considered related to study treatment. Nine subjects (4 in Group A and 5 in Group C) had pulmonary or cardiac events that contributed to their death: pulmonary hemorrhage (3 subjects); dyspnea (2 subjects); and circulatory collapse, bronchopneumonia, lung infection, and respiratory failure (1 subject each).

Serious Adverse Events: Serious adverse events were reported in 37% of subjects in Group A, 24% of subjects in Group B, and 31% of subjects in Group C. The higher number of Grade 3-5 serious adverse events in the combination arm is predominantly due to Grade 3 neutropenia, Grade 3-4 thrombocytopenia, and Grade 4 hyponatremia. The most frequently reported (>3% of subjects) serious adverse events were dyspnea (4%), febrile neutropenia (3%), pyrexia (3%), and vomiting (3%). Drug-related serious adverse events were reported in 29% of subjects in Group A, 14% of subjects in Group B, and 4% of subjects in Group C. The most common drug-related serious adverse events were febrile neutropenia and vomiting, each reported in 4 subjects (3%).

Other Significant Adverse Events: The incidence of adverse events leading to treatment discontinuation was 19% for Group A, 14% for Group B, and 10% for Group C. The most common adverse event leading to treatment discontinuation was dyspnea (3 subjects). Four subjects (3 in Group A, 1 in Group C) had nervous system disorders (peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy, and paresthesia) that resulted in discontinuation of study treatment. For all 4 subjects, the investigator considered the nervous disorder to be related to VELCADE. The polyneuropathy also was considered possibly related to Alimta. Alimta-related adverse events resulted in treatment discontinuation for 10% of subjects in Group A and 14% of subjects in Group B. The most common of these events were asthenia, febrile neutropenia, and thrombocytopenia (2 subjects each). VELCADE-related adverse events resulted in treatment discontinuation for 12% of subjects in Group A and 2% of subjects in Group C. The most common of these events was thrombocytopenia (2 subjects). The most common treatment-emergent adverse events leading to dose modification, cycle delay, or missed doses were thrombocytopenia and neutropenia.

Laboratory Abnormalities: Increased neutropenia, leukopenia, and thrombocytopenia was reported in Group A compared to Groups B and C.

FACT/GOG-Ntx Scores: The baseline FACT/GOG-Ntx scores were similar among the 3 treatment groups, and each group did not show any significant changes with treatment.

CONCLUSIONS: Treatment with combined VELCADE and Alimta did not show an improvement in ORR, TTP, PFS, and OS compared to Alimta alone. The main drug-related Grade 3-5 toxicities, thrombocytopenia and neutropenia, were generally clinically manageable. The results of this study do not show sufficient clinical activity in the VELCADE plus Alimta combined group compared to the Alimta alone or VELCADE alone groups to justify proceeding to a Phase 3 investigation with this combination in patients with advanced NSCLC.

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