SYNOPSIS

Name of Company: Nerviano Medical Sciences **Name of Finished Product:** Not Applicable **Name of Active Ingredient:** PHA-739358	*(For National Authority Use only)*
Title of Study: An Exploratory Phase II Study of PHA-739358 in Patients with Multiple Myeloma Harboring the t (4;14) translocation with or without FGFR3 Expression.	
Protocol Number: AURA-6202-011	
Investigator(s): 1) Prof. Rafael Fonseca MD; 2) Dr. Seema Singhal MD; 3) Prof. Jean Luc Harousseau MD; 4) Prof. Thiérry Facon MD	
Study Centers: The study was conducted in USA and in France at 4 centers, namely: 1) Mayo Clinic Arizona, Scottsdale-USA 2) The Robert H. Lurie Comprehensive Cancer Center – Northwestern University – Chicago-USA 3) Dept. of Hematology – University Hospital Hotel-Dieu, Nantes-France 4) Service des Maladies du Sang – Hopital Huriez, University Regional Hospital of Lille-France	
Publication Reference: Not Applicable	
Studied Period (Years): Date of first subject enrollment: 14 Jan 2009 Date of last subject completed: 12 Jun 2009	**Phase of Development**: Phase II
Objectives: **Primary:** To determine the anti-tumor activity of PHA-739358 in patients with Multiple Myeloma harboring the t(4;14) translocation. **Secondary:** To define the safety profile of PHA-739358 in Multiple Myeloma patients; to investigate the inhibition of Aurora kinase and FGFR3 signaling in bone marrow plasma cells.	
Methodology: This was a Phase II exploratory, open-label study designed to determine the anti-tumor activity of PHA-739358 in adult patients with Multiple Myeloma harboring the t(4;14) translocation, who had a history of at least two prior lines of treatment for the disease. The primary endpoint of the study was the response rate, consisting in minor responses or better. The protocol was amended to introduce the assessment of left ventricular ejection fraction by transthoracic echocardiography (TTE) before the infusion of PHA-739358 on Day 1 of each cycle. The protocol received a total of three Amendments (Amendment # 1 dated 21 April 2008, to incorporate changes requested by the French Health Authorities – Amendment # 2 dated 23 May 2008, to incorporate changes requested by the Hematology Research Committee of the Mayo Clinic Arizona and Amendment # 3 dated 29 September 2008 valid for Mayo Clinic only, to incorporate a change requested by the Investigational Review Board (IRB) of the Mayo Clinic Scottsdale - Arizona). To patients who did not present any grade 3 non-hematological toxicity and with a sub-optimal response (MR), a dose intensification with weekly administration would have been proposed (330 mg/m^2 on Days 1, 8, 15 and 22 every 4 weeks), after discussion between the Investigator and the Sponsor. Patients could continue on study treatment for a maximum of 8 cycles, or until disease progression, refusal, consent withdrawn, or the	

Name of Company: Nerviano Medical Sciences **Name of Finished Product:** Not Applicable **Name of Active Ingredient:** PHA-739358	*(For National Authority Use only)*

occurrence of unacceptable toxicity, whichever occurred first. Patients who benefited from therapy might have continued beyond the 8 cycles upon agreement with the Sponsor.

Safety assessments (vital signs, hematology, blood chemistry, urinalysis) were to be performed at baseline and some of them also more frequently at different time points during the treatment period, depending on the parameter, and at the end of treatment. To monitor cardiac events, a 12-lead ECG was to be performed at screening visit, on Day 1 at the end of infusion of every odd cycle, and at the end of treatment. A TTE was scheduled at screening, on Day 1 of every even cycle and at the end of treatment visit. Such exam had to be repeated more frequently on treatment if clinically indicated. Patients showing left ventricular ejection fraction (LVEF) value < 35% had to undergo a confirmatory multi gated acquisition (MUGA) scan. Patients were to be followed for adverse events (AE) from the signing of the informed consent up to 28 days after the last dose of study treatment or until all drug-related toxicities had resolved or an alternative anticancer therapy was started. Tumor response calendar was dependent upon the type of test. Bone marrow exam had to be performed at baseline, during treatment as clinically indicated, and at end of treatment and at follow-up every 3 months for patients who were not progressing at time they went off treatment. Myeloma parameters (serum protein electrophoresis, serum immunofixation, urine total volume, urine total protein, creatinine clearance, urine protein electrophoresis and urine immunofixation) had to be performed at baseline, at the end of each cycle only in patients who resulted positive at baseline and at the end of treatment and in the follow-up every 3 months for patients who were not progressing at time they went off treatment. Bone marrow for biomarker evaluation was to be obtained for assessment of inhibition of Aurora kinase and FGFR3 signaling at baseline and at cycle 1 at the end of Day 1 infusion.

Number of Subjects (Planned and Analyzed): Originally a sample size of approximately 20 patients was anticipated. Finally a total of 7 patients were enrolled and 6 treated.

Diagnosis and Main Criteria for Inclusion: Adult consenting patients (age ≥ 18 and ≤ 75 years) with confirmed diagnosis of active Multiple Myeloma relapsed or refractory to at least two prior lines of treatment, including two of the three following drugs : bortezomib, lenalidomide and thalidomide, with t (4;14) translocation and with current measurable disease defined by at least one of the following three measurements : serum M-protein ≥ 1g/dl or urine M-protein ≥ 200 mg/24 h or bone marrow plasma cells ≥ 30 %. At least 4 weeks had to have elapsed between the end of the last therapy and the date of study entry. Other main selection criteria included Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, baseline laboratory data indicating acceptable liver, and renal function, life expectancy of at least 3 months, resolution of all acute toxic effects (excluding alopecia) of any prior surgery, radiotherapy, radio-surgery or chemotherapy to NCI CTCAE (version 3.0) Grade ≤ 1 (exception : stable, grade 2 neuropathy was permitted). Patients with non-detectable M-component (non-secretory myeloma), active uncontrolled infection, known history of human immunodeficiency virus (HIV) infection, uncontrolled hypertension with blood pressure exceeding 160/100 mmHg, with abnormal LVEF (< 50% by TTE performed within the previous 2 weeks), with cardiac dysrhythmias Grade ≥ 2 according to NCI CTCAE version 3.0, with major surgeries within 4 weeks from study treatment start or not fully recovered from any previous surgical procedure, with significant cardiovascular disease or a major thromboembolic event in the previous 6 months, pregnant and breast feeding females were to be excluded.

Test Product, Dose and Mode of Administration, Batch Number: PHA-739358 was administered as 6-h IV infusion at 330 mg/m^2 on Days 1, 8, and 15 every 4 weeks. Dose intensification with weekly administration was proposed for patients who did not present any Grade 3 non-hematological toxicity and with a sub-optimal response defined as Minor Response (MR), after discussion between the Investigator and the Sponsor. prophylactic use of hematopoietic growth factors was allowed, if clinically indicated, according to the

Name of Company: Nerviano Medical Sciences **Name of Finished Product:** Not Applicable **Name of Active Ingredient:** PHA-739358	*(For National Authority Use only)*

Investigator's judgment.

PHA-739358 batch numbers used in the study: N0800173 – N0800174 – N0800427.

Reference Therapy, Dose and Mode of Administration, Batch Number: Not Applicable

Duration of Treatment: Each patient received PHA-739358 for a maximum of 8 cycles, or until disease progression, patient refusal, consent withdrawal, or the occurrence of unacceptable toxicity. Patients who benefited from the treatment could continue beyond the 8 cycles upon agreement with the Sponsor.

Endpoints and Criteria for Evaluation:

Efficacy:

- Response rate, as defined by the International Myeloma Working Group uniform response criteria for Multiple Myeloma (Durie BG, Harousseau JL, Miguel JS, Bladé J et Al." International uniform criteria for multiple myeloma "International Myeloma Working Group. Leukemia 2006, 1-7). Modified International Working Group uniform response criteria were applied for defining Minor response (MR).

Safety:

- Type, frequency, severity, timing of AEs and laboratory abnormalities.

Other:

- Duration of response, time to disease progression.
- Inhibition of Aurora kinase and FGFR3 signaling in bone marrow plasma cells.

Statistical Methods: All patients receiving at least one treatment dose were to be considered as target population. Descriptive statistics and patients' data listings were to be used in the characterization of patients' disposition, baseline characteristics, treatment exposure, efficacy and safety variables. Point estimates and 95% confidence interval of response rate (Minor Response or better) were to be provided. Duration of response, time to disease progression were to be analyzed by the Kaplan-Meier method: summary of descriptive statistics including range and median values were to be provided. AEs and hematological and biochemical toxicity were graded according to the NCI CTCAE version 3.0. AEs were coded based on the Medical Dictionary for Regulatory Activities (MedDRA).

SUMMARY OF RESULTS:

Disposition of Subjects and Baseline Characteristics: Seven patients were registered in this study and 6 resulted treated. The study was discontinued mainly due to the objective difficulty in finding eligible patients vis-à-vis of the received recruitment limitations on the disease stage and treatment population of patients. The most frequent reason for study discontinuation was lack of efficacy (three patients started new therapy, one progressed, one went off due to investigator's decision and one died). Of the six treated patients, one had SD as best overall response at cycle 1. All treated patients had confirmed diagnosis of multiple myeloma; according to the Durie and Salmon Classification, two patients had Stage I-relapsed and three patients had Stage III-relapsed; for one patient the information on stage could not be obtained. Most enrolled patients were males (5 males, 2 females). Three patients were older than 65 years of age and three younger than 65 years of age, all patients were of white race. Fifty per cent of treated patients had ECOG Performance Status of 0 at entry, for the other fifty per cent the ECOG Performance Status at entry was 1. Prior anticancer therapies were systemic therapy and transplantation for four patients and systemic therapy alone for two. All treated patients

Name of Company: Nerviano Medical Sciences **Name of Finished Product:** Not Applicable **Name of Active Ingredient:** PHA-739358	*(For National Authority Use only)*

resulted harboring the t(4;14) translocation at entry.

Treatment Exposure:

Overall, patients received 13 cycles with a median cumulative dose of 1498.1 mg/m^2 (range 330.8-2,347.0 mg/m^2); median number of cycles was 2 (range 1-3) and median relative dose intensity was 64.5/% (range 33.4-83.7%).

Efficacy Results:

No objective response was reported. Disease stabilization was observed in one patient (16.7 %) at the first cycle of treatment. At pretreatment, bone marrow collection for FGFR3 positivity assessment was performed for four patients. In the sole patient with at least one post-baseline check available a decrease from 100% to 68% of FGFR3 positive cells was shown. As far as H3 and STAT5 phosphorylation in bone marrow samples resulted available only for two patients. The available data were too limited to draw any conclusion.

Safety Results:

All the 6 treated patients were evaluable for safety. Cough and fatigue were the two most frequent non hematologic adverse events on treatment affecting at least two different patients (33.3 %); cough reached at worst CTC grade 1 in both patients and was considered as possibly drug related in one patient only, while fatigue reached CTC grade 2 in both patients and was unlikely related in one of them only. Two CTC grade 3 adverse events were considered as possibly related to study drug and affected two distinct patients: one was febrile neutropenia considered as serious, which determined dose treatment modification/delay and subsequently recovered, the other one was acute renal failure, that was assessed as non serious by the Investigator, causing treatment dose change/delay and persisting nonetheless. As to the drug-related adverse events ranking, it is not possible to indicate which events resulted mostly present, because the reported occurrences developed in a total of three patients overall and were all eight different in type and characteristics. Four serious adverse events were reported and only one of them considered as drug related. There were no drug-related adverse events leading to treatment discontinuation. Creatinine, alkaline phosphatase and albumin were the only blood chemistry tests showing modifications from baseline during treatment administration. All but blood creatinine had absolute increases of one CTC grade category only and reached at maximum CTC Grade 2; blood creatinine raised from CTC grade 0 at baseline to CTC grade 3 at cycle 1 in a 70 years old female patient, who received only one cycle of therapy. Hematologic toxicity was a common finding, and mainly represented by CTC grade 3-4 leucopenia and neutropenia during treatment. No significant changes in the values of blood pressure were reported in the treated patients while on study. LVEF decrease by 43.5 % vs. baseline (LVEF value of 34 vs. 78) was reported in one patient after 1 week since treatment start, subsequent ECHO measurement after almost two weeks since then showed LVEF of 55 %, so within normal limit. One patient died due to disease progression 13 days since last study drug administration.

Pharmacokinetics Results:

No pharmacokinetics analysis planned.

CONCLUSIONS:

In conclusion, the study had to be discontinued before hand due to the recruitment hurdles encountered linked to the strict limitations allowed for conducting the study. Toxicities observed within the present study were consistent with preclinical findings, manageable and reversible, despite the limited number of treated patients. Hematological toxicity has been the main PHA-739358- induced toxicity, mainly represented by leucopenia and neutropenia. No objective response could be reported.

Date of the Report: 30 - September - 2010.