SYNOPSIS

Name of Company: Nerviano Medical Sciences **Name of Finished Product:** Not applicable **Name of Active Ingredient:** Milciclib Maleate (PHA-848125AC)	*(For National Authority Use only)*

Title of Study: Phase II study of PHA-848125AC as second line-treatment in pemetrexed pre-treated malignant pleural mesothelioma patients

Protocol Number: CDKO-125a-005

Investigators: 1) Armando Santoro; 2)Paolo Bidoli; 3) Mario Botta; 4) Adolfo Favaretto; 5) Manlio Mencoboni; 6) Silvia Novello; 7) Marcello Tiseo.

Study Centers:
All the study sites were located in Italy:
1) Coordinating Site: Istituto Clinico Humanitas IRCCS, Rozzano (MI); 2) Azienda Ospedaliera San Gerardo di Monza, Monza (MB); 3) Ospedale Santo Spirito, Casale Monferrato (TO); 4) Istituto Oncologico Veneto IRCCS, Padova; 5) Ospedale Villa Scassi, Genova; 6) Azienda Ospedaliera San Luigi Gonzaga, Orbassano (TO); 7) Azienda Ospedaliera Università di Parma, Parma.

Publication Reference:

Studied Period (Years):	**Phase of Development:**
02 March 2009 09 February 2011	Phase II

Objectives:

Primary: To assess the antitumor activity in terms of TTP of PHA-848125AC as second-line treatment in pemetrexed-pretreated patients with MPM.
Secondary: To assess additional measures of tumor control to further characterize the efficacy profile of PHA-848125AC in MPM patients; to evaluate the safety profile of repeated administrations of PHA-848125AC in MPM patients; to monitor blood levels of PHA-848125AC through a limited PK sampling procedure.

Methodology: This was a single-arm, single-stage, open-label, multicenter, phase II study of PHA-848125AC in adult patients with malignant pleural mesothelioma (MPM) previously treated with a pemetrexed-containing chemotherapy (only one prior chemotherapy regimen allowed).

Number of Subjects (Planned and Analyzed):
A sample size of 44 evaluable patients was anticipated for the primary efficacy analysis of this study. Overall, 38 patients were enrolled and treated.

Diagnosis and Main Criteria for Inclusion:

Subject Inclusion Criteria

1. Signed and dated IRB/IEC-approved Informed Consent
2. Histologically or cytologically proven diagnosis of Malignant Pleural Mesothelioma (MPM), inoperable, in relapse after failure of prior pemetrexed-containing treatment (only one prior chemotherapy regimen allowed)
3. Presence of unidimensionally and/or bidimensionally measurable disease. Patients undergoing palliative radiation therapy for painful lesions were allowed to enter the study, provided that they had measurable

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disease outside the irradiated site

4. No or asymptomatic pleural effusion. Patients with symptomatic pleural effusions could be enrolled provided that they had their effusions drained prior to enrollment on the clinical trial
5. Age ≥ 18 years
6. ECOG (WHO) performance status 0-1
7. Estimated life expectancy of at least 3 months
8. Negative pregnancy test (if female in reproductive years)
9. Agreement upon the use of effective contraceptive methods (hormonal or barrier method of birth control, or abstinence) prior to study entry and for the duration of study participation, if men and women of child producing potential
10. Adequate liver function:
    - Bilirubin ≤ upper limit of normal (ULN)
    - Albumin ≥ 3.0 g/dL
    - AST (SGOT), ALT (SGPT) ≤2.5 ULN (if liver metastases were present, then ≤ 5 ULN was allowed)
    - Alkaline phosphatase ≤ 2.5 ULN (if liver and/or bone metastases were present, then ≤ 5 ULN was allowed)
11. Adequate renal function:
    - Serum creatinine ≤ ULN
12. Adequate hematologic status:
    - ANC ≥ 1,500 cells/mm^3
    - Platelet count ≥ 100,000 cells/mm3
    - Hemoglobin ≥ 9.0 g/dL
13. At the time of treatment start, at least 4 weeks must had elapsed since completion of prior chemotherapy, surgery, radiotherapy (provided that no more than 25% of bone marrow reserve had been irradiated)
14. With the exception of alopecia, resolution of all acute toxic effects of any prior surgery, radiotherapy or chemotherapy to NCI CTC (Version 3.0) grade ≤ 1 and to the baseline laboratory values as defined in Inclusion Criteria Number 10, 11, 12
15. Able and willing to comply with scheduled visits, therapy plans, and laboratory tests required in this protocol
16. Capability to swallow capsules intact (without chewing, crushing, or opening).

Subject Exclusion Criteria

1. Any of the followings in the past 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis
2. Grade >1 retinopathy
3. Known brain metastases
4. Major surgery, other than diagnostic surgery, within 4 weeks prior to treatment
5. Active, uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy
6. Known infection with HIV, active hepatitis B or hepatitis C

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7. Pregnant or breast feeding women
8. Previous (within the last 5 years) or current malignancies at other sites, except for adequately treated basal cell or squamous cell skin cancer or in situ carcinoma of the cervix uteri
9. Current enrollment in or participation in another therapeutic clinical trial within 4 weeks preceding treatment start
10. Diabetes mellitus uncontrolled
11. Gastrointestinal disease (e.g. Crohn's disease, ulcerative colitis, or short gut syndrome) that would have impacted on drug absorption
12. Patients under treatment with anticoagulants or with coagulation disorders or with signs of hemorrhage at baseline
13. Patients with previous history or current presence of neurological disorders, including epilepsy (although controlled by anticonvulsant therapy), Parkinson's disease and extra-pyramidal syndromes
14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that might have increased the risk associated with study participation or might have interfered with the interpretation of study results and, in the judgment of the Investigator, would have made the patient inappropriate for entry into this study or could have compromised protocol objectives in the opinion of the Investigator and/or the Sponsor.

Test Product, Dose and Mode of Administration, Batch Number:

PHA-848125AC is formulated as oral 10 mg, 50 mg and 100 mg capsules to be swallowed intact (without chewing, crushing or opening). The compound was administered once daily at the flat dose of 150mg/day for 7 days on / 7 days off in a 2-week cycle. The batch numbers used for this study were: N0900095; N0901366; N0902245; N1000232; N1000499; N1001720 (50 mg caps); N0900096; N0901367; N0902246; N1000234; N1000500; N1001721 (100 mg caps). No batches of 10 mg strength were used.

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

Duration of Treatment: Patients were to continue on study treatment until disease progression, patient refusal or withdrawal of patient consent, or the occurrence of unacceptable toxicity and were to be followed up for survival up to the end of the study and in any case for no more than 2 years from the end of treatment.

Endpoints and Criteria for Evaluation:
The primary endpoint was to be based on the TTP, i.e. the time from the date of treatment start to the date of first documentation of objective tumor progression, objective tumor recurrence or of death due to progressive disease (PD), whichever comes first. The primary efficacy analysis was to be performed on the proportion of evaluable patients in a progression free-status at 12 weeks (i.e: 12-week PD-free rate).
Secondary endpoints:
-Confirmed objective tumor response according to RECIST [Therasse P. et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst. 2000; 92 (3):205-216] and Modified RECIST criteria [Byrne MJ, Novak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol 2004;15:257-260];
- Disease Control Rate (Confirmed Objective Response Rate + SD rate)
- Time to Tumor Progression (TTP) overall profile;
- Duration of Response;
- Overall Survival (OS), i.e. the time from the date of treatment start to the date of death from any cause; in the

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absence of documentation/confirmation of death, survival time was to be censored at the date of the last visit or contact documenting that the patient was still alive.
- Evaluation of serum marker (osteopontin and soluble mesothelin-related proteins) levels to investigate the potentially prognostic value of baseline serum marker levels on TTP and OS, if clinically indicated
- Overall safety profile, evaluated on the basis of laboratory and clinical safety parameters (i.e. hematology and blood chemistry, urinalysis, vital signs, ECG, ophthalmologic examinations and adverse events emerging during the trial). The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0 will be used for the severity grading of adverse events and hematological and blood chemistry abnormalities
- PHA-848125AC plasma levels.

Statistical Methods:
For the primary efficacy analysis, the PD-free rate at 12 weeks was to be calculated as the proportion of evaluable patients known to be progression-free at ≥ 12 weeks out of the total number of evaluable patients. The following decision rule was to be applied: if ≥ 20 / 44 evaluable patients, were progression-free at ≥ 12 weeks, then the null hypothesis of a 12-week PD-free rate as low as 35.4% was to be rejected at the 1-sided α-level of 0.10.
Supportive analysis of the primary endpoint was to be conducted in the treated patients population and in the evaluable patient population and was to include the estimation of the 12-week PD-free rate and exact two-tail 90% confidence interval and the estimation of the PD curve by Kaplan-Meier method. The efficacy endpoints including the confirmed objective response rate, the disease control rate, the duration of response, and the overall survival were to be descriptively analyzed in both the evaluable and the treated patient population. Kaplan Meier estimations were to be generated and plotted to evaluate the overall survival curve. Serum osteopontin and soluble mesothelin-related proteins levels were to be descriptively analyzed at each assessment timepoint. The Cox proportional hazard model was to be used to examine associations between baseline serum marker levels and the endpoints of TTP and OS. Exploratory analysis (Chi-square test, Cox's proportional hazard model) on the relationship between p16/CDKN2A gene status and treatment efficacy variables (e.g. tumor response, TTP, OS) were to be performed, if sufficient data were collected. Patients' baseline characteristics, treatment exposure and safety data were to be analyzed in the treated patient population. Descriptive statistical analyses and individual data listings were to be used to report all collected data including patient disposition, protocol deviations, baseline characteristics, treatment exposure, efficacy, and safety data.

Patient Populations: *Screened Patients*: This population included all patients who were screened for potential eligibility for the trial, regardless of whether or not they were to be enrolled in the study. This population was to be evaluated in the analysis of patients' disposition.
Enrolled Patients: This population included all the enrolled patients, regardless of whether they received the study drug or not. This population was to be evaluated in the analysis of patients' disposition.
Treated Patients: The treated patient population consisted of all enrolled patients who had actually received at least one study drug administration. This population was to be evaluated in the analysis of patient disposition, baseline characteristics, treatment efficacy and safety and treatment exposure.
Patients Evaluable for Efficacy Analysis: This definition included the patient population for the primary efficacy analysis of 12-week PD-free rate and consisted of all eligible and treated patients who had fulfilled the following additional conditions: a) They had received at least 80% of drug in the first two cycles overall; b)They had undergone baseline and ≥1 on-treatment tumor/oncologic assessments or had died before tumor

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re-assessment.

SUMMARY OF RESULTS:

Disposition of Subjects and Baseline Characteristics:

In the present trial, 38 patients (28 males and 10 females, with median age of 64.0 years) were enrolled and treated with of PHA 848125AC for 7 days on/7 days off, in a 2-week cycle at the flat dose of 150 mg/day. All patients had a diagnosis of malignant pleural mesothelioma (MPM) and had received one line of systemic prior therapy including pemetrexed. Seven patients also received one additional line of prior systemic therapy in neo-adjuvant or adjuvant setting. Fifteen patients had metastatic disease at study entry and the most frequent sites of metastasis were lymph nodes (23.7%) lung (10.5%) and liver (5.3%). Gene p16/CDKN2A status at baseline was assessed in 9 patients, and methylation only was evaluated. Serum marker (osteopontin and SMRP) levels at baseline were assessed in 32 patients. ECOG performance status was reported in all patients and scored 0 (25 pts) and 1 (13 pts). The reason for treatment discontinuation (off-treatment reason) was progression of the disease in 33 patients (86.8%) and adverse event in 5 patients (13.2%) while the off-study reasons were death (23 pts, 60.5%), FU completed (1 pt, 2.6%), lost to FU (4 pts, 10.5%) and Sponsor's decision (10 pts, 26.3%). When it was evident that the study was not successful for the primary efficacy endpoint, the Sponsor decided not to go ahead in fully exploring the survival status (to be monitored up to 2 years after the last dose in all patients). For patients still in the 2 year follow up period at that time, collection of survival data was censored at the date of 31 March 2011.

Treatment exposure: PHA 848125AC was admistered for 7 days on/7 days off, in a 2-week cycle at the flat dose of 150 mg/day, with a median dose intensity (i.e: median mg/wk) of 514.3 mg (range 245.0-537.8). A total of 181 cycles were administered: the median number of cycles per patient was 3 (range 1 – 19).
Treatment modifications (i.e: delays/reductions) were implemented at cycle start and/or intra cycle in 21 patients over 35 cycles. *Hematologic toxicity* (i.e: neutropenia and anemia) caused modifications in 4 pts over 4 cycles. *Non hematologic toxicity* caused modifications in 11 patients over 15 cycles) and consisted of anorexia, asthenia, cough, diarrhoea, dyspnoea, fatigue, hypertension, nausea, pain, pleural effusion, syncope, tremor, transaminase increase, vertigo, vomiting, Treatment was modified due to *other reasons* (logistical) in 11 patients over 16 cycles. Treatment compliance: over a total number of 181 cycles, the percentage of the administered *vs* scheduled dose by cycle was 100% in 154 cycles (out of 181), more between 80 and 100% in 4 cycles, between 50 and 80% in 22 cycles and less than 50% in one cycle only.

Efficacy Results:

PHA-84815AC failed to meet protocol criteria for efficacy in the identified patient population (i.e. second line MPM pemetrexed-pretreated patients). In fact, at least 20/44 evaluable patients were required to be PD-free at 12 weeks from treatment start to reject the null hypothesis, this corresponding to a PD-free rate at 12 weeks ≥ 45.5% and to a median TTP ≥10.5 weeks. Actually only 6 patients resulted to be successes (i.e: PD-free at 12 weeks), out of 32 evaluable patients (18.8%; 90% CI, 8.5 - 33.7) and median TTP resulted to be 6.7 weeks (range 5.0 – 38.6 weeks, 95% CI, 5.7 – 12.1).
Neither CRs nor PRs were reported; SD was reported as best overall response in 13 patients (40.6%). Prolonged SDs (≥ 8 months) were observed in 2 patients, i.e: No. 0024 and 0038 (SD lasting for 8.9 and 8.7 months, respectively). In the evaluable patients population the median overall survival was 10.1 months (range 1.4 – 20.6).
Serum markers, although with the caveat of the limited number of observations, a trend towards a longer TTP and OS seems present in association with lower baseline levels of osteopontin, suggesting a somewhat unfavorable prognostic value for high levels of this marker for MPM patients. For SMRP, the data available do not allow any specific correlation with baseline levels.

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No correlation between baseline p16/CDKN2A gene status and treatment efficacy variables was possible, due to the very limited number of observations.
Supportive analyses in the treated patients population are consistent with the results obtained in the evaluable patients population (PD-free rate: 15.8%; median TTP: 6.7 weeks; median OS: 10.1 months).

Safety Results:
All patients experienced at least 1 AE in the first or subsequent cycles and 36 patients presented drug related events. The most frequent AEs (frequency of ≥ 10%), were nausea (73.7%, drug related 71.1%), diarrhoea (55.3%, drug related 50.0%), asthenia (52.6%, all drug related), tremor (47.4%, all drug related), vomiting (42.1%, all drug related), dyspnoea (28.9%, none drug related), cough (23.7%, none drug related), anorexia (21.1%, drug related 18.4%), constipation (18.4%, drug related 13.2%), fatigue (18.4%, all drug related), chest pain and pain NOS (15.8%, none drug related), vertigo (13.2%, all drug related) and pyrexia (13.2%, drug related 10.5%).
No CTC Grade 4 events were observed. CTC Grade 3 events were reported by 13 patients (34.2%) and in 5 (13.2%) were drug related; they consisted in dyspnoea (4 cases, 10.5%, none drug related), nausea, diarrhoea and fatigue (2 cases each, 5.3%, all drug related), pleural effusion (5.3%, none drug related), vomiting and vertigo (1 case each, all drug related), chest pain, pain NOS, anaemia, abdominal pain, ascites, central nervous system lesion, glycosuria, oxygen saturation decreased and thrombosis (1 case each, none drug related).
Only one CTC Grade 5 event (general physical health deterioration) was reported in one patient and was considered not drug related.

Ocular and CNS toxicities were monitored. One patient discontinued treatment after 2 cycles due to CTC Grade 2 retinal exudates and a Grade 2 worsening in ERG parameters for left eye (reduced B wave amplitude). Both events were considered as probably related to study medication.
Neurological toxicity occurred in 71.1% of the treated population as CTC Grade 1-2 events, all drug related; the most frequent events were represented by tremor (18 patients, 47.4%, maximum CTC Grade 2 in 11%), dizziness (3 patients, 7.9%, maximum CTC Grade 2 in one case), dysgeusia (3 patients, 7.9%, maximum CTC Grade 1), and paresthesia (3 patients, 7.9%, maximum CTC Grade 2 in one case).

Hematological toxicity (36 patients evaluable) was predominantly mild/moderate, with grade 3 findings in a very limited number of patients (lymphocytopenia in 8 cases, 22.2%, and anemia, WBC decreases, neutrophils decrease in 1 patient each). Blood chemistry tests (31-36 patients evaluable, depending on the parameter investigated) were in majority of grade 0 or 1 in severity, sporadically of CTC Grade 2. Creatinine maximum grade 2 was reported in 1 patient. Grade 3 ALT, amylase, magnesium and potassium elevations were observed in one case each.

Four patients died on study (i.e. within 28 days after the last treatment dose). All the occurrences were caused by disease progression of the underlying malignant pleural mesothelioma and were considered unrelated to the study treatment.
Company Pharmacovigilance was notified of the occurrence of 14 SAEs in 9 treated patients. All the SAEs were classified as unrelated to the study medication.
No important effect of the study drug on blood pressure was evident: blood pressure increases were only occasionally observed. No significant abnormalities in ECG tracings were observed on treatment; CTC Grade 1 ventricular extrasystoles and Grade 2 tachycardia were reported as adverse events in 1 patient each. No ECOG PS scores >1 were reported during treatment in any patient.

In summary, overall, safety results confirm the toxicological profile of the compound emerged from previous

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clinical experience with the same dose-schedule as a single agent (i.e. 150 mg/day 7 days on / 7 days off). The most frequent drug-related AEs (frequency of ≥ 10%), were nausea (71.1%), asthenia (52.6%), diarrhoea (50.0%), tremor (47.4%), vomiting (42.1%), anorexia and fatigue (18.4% each), constipation and vertigo (13.2% each) and pyrexia (10.5%). Drug-related CTC Grade 3 events were reported in 13.2% of patients, i.e. nausea, diarrhoea and fatigue (2 cases each), vomiting and vertigo (1 case each).
No drug related CTC Grade 4-5 events occurred. No drug-related SAEs were reported.
Side effects were generally transient and manageable.

Hematological toxicity was predominantly mild/moderate, with Grade 3 findings in a very limited number of patients (lymphocytopenia in 22.2% of evaluable patients, and anemia, WBC decreases, neutrophils decrease in 1 patient each). Blood chemistry abnormalities were mostly of Grade 0-1 in severity, with sporadic cases of Grade 2 alterations and 4 occurrences of Grade 3 abnormalities, not clinically relevant, represented by ALT, amylase, magnesium and potassium elevations. Creatinine of maximum Grade 2 was reported in 1 patient only.
No important effects on blood pressure, ECG, coagulation parameters emerged during treatment, nor significant ocular events, with the exception of a patient discontinuing treatment because of a worsening of the ERG evaluation and retinal exudates after 2 cycles of treatment.

Pharmacokinetic Results:
Plasma levels of PHA-848125 and its metabolite NMS-867734 were monitored on Cycle 3, through a limited PK blood sampling (on Day 1, before and 2 hours after PHA 848125AC administration, and one day between Day 11 and Day 14). At least one plasma sample was available from 29 out of the 38 treated MPM patients (76.3%) to be analyzed for PK assessment.
At the pre-dose of the third cycle of treatment, PHA-848125 was detectable in all pre-dose samples at the average level of 0.0804 µM. At 2 hours post-dosing, the drug reached a mean ± SD concentration of 0.547 ± 0.397 µM. In plasma samples collected during the resting period (anytime between Day 11 and Day 14), PHA-848125 level was on average 0.160 µM, ranging between 0.00116 and 1.15 µM.
At the pre-dose of the third cycle of treatment, plasma concentration of NMS-867734 was on average 0.0219 µM. At 2 hours post-dosing, the mean ± SD concentration of the metabolite was 0.138 ± 0.0951 µM. In plasma samples collected during the resting period, the metabolite level was on average 0.0427 µM. At each collection time, the metabolite to parent drug mean concentration ratio was maintained around 25-27%.
Overall, plasma levels of parent drug and metabolite measured in this study are comparable to those previously obtained in the Phase I study CDKO-125a-001 at the same dose-schedule, confirming the reliability of the pharmacokinetic profile of the compound.

CONCLUSIONS:
The primary endpoint was not met in this study and PHA-848125AC at the adopted dose-schedule (i.e.: 150 mg/day for 7-day on/ 7-day off q2wks) did not demonstrate sufficient activity as a single agent in second line therapy of MPM patients.

The overall safety profile of the compound was confirmed, as well as the reliability of its pharmacokinetic profile; this indicates that the adopted dose-schedule is well tolerated, with no new emerging safety issues, and therefore could be further evaluated in other tumor types.

Date of the Report:
30 March 2012