Synopsis of Study Report

Company:	Tabular Format Referring to part of the Dossier	(For National Authority Use only)
Name of Finished Product:	Volume:	
Name of Active Substance(s):	Page:	

Sponsor:	MolMed S.p.A.
Investigational Product (Name):	NGR-hTNF
Indication:	Advanced or metastatic malignant pleural mesothelioma (MPM)
Title of the Study:	NGR010: A phase II study of NGR-hTNF administered as single agent every 3 weeks or weekly in patients affected by advanced or metastatic malignant pleural mesothelioma previously treated with no more than one systemic therapeutic regimen
Investigators:	Prof. Federico Caligaris Cappio, Prof. Armando Santoro, Dr. Filippo De Braud, Dr. Nicoletta Zilembo
Study centre(s):	HSR Milan, Coordinating Center (I), ICH Rozzano (I), IEO Milan (I), INT Milan (I)
Publication (reference):	Gregorc V, Zucali P A, Santoro A, et al. (2011) Phase II Study of Asparagine-Glycine-Arginine–Human Tumor Necrosis Factor alpha, a selective vascular targeting agent, in previously treated patients with malignant pleural mesothelioma. J Clin Oncol 28(15):2604-2611
Phase of development:	Phase II
Study period (years): **(date of first enrolment):** **(date of last completed):**	3 years May 14th, 2007 September 14th, 2010
Objectives:	Primary: antitumour activity defined as progression free survival (PFS) Secondary: Tumor Growth Control Rate (TGCR) according to Response evaluation criteria in solid tumors (RECIST); Overall Survival (OS); Experimental imaging study (Dynamic contrast-enhanced magnetic resonance imaging, DCE-MRI); Pharmacokinetics in patients treated with weekly schedule; Safety
Methodology:	Single arm, open label, non randomized study
Number of patients:	57 (2 patients untreated, 41 treated with a triweekly schedule + 14 treated with a weekly schedule)
Diagnosis and main criteria for inclusion:	Patients ≥18 years affected by malignant pleural mesothelioma previously treated with no more than one systemic therapeutic regimen; Histologically or cytological confirmed malignant pleural mesothelioma of any of the following subtype: epithelial, sarcomatous, mixed;

Synopsis of Study Report

Company: Name of Finished Product: Name of Active Substance(s):	Tabular Format Referring to part of the Dossier Volume: Page:	(For National Authority Use only)

Diagnosis and main criteria for inclusion:	Prior intrapleural cytotoxic agents including bleomycin not considered systemic chemotherapy; ECOG Performance status 0 – 2; Adequate baseline bone marrow, hepatic and renal function, defined as follows: - Neutrophils > 1.5 x 10^9/L and platelets > 100 x 10^9/L - Bilirubin < 1.5 x ULN - AST and/or ALT < 2.5 x ULN in absence of liver metastasis - AST and/or ALT < 5 x ULN in presence of liver metastasis - Serum creatinine < 1.5 x ULN Absence of any conditions in which hypervoleamia and its consequences (e.g. increased stroke volume, elevated blood pressure) or haemodilution could represent a risk for the patient (take as reference "Technical data sheet human albumin" specifically used in Pharmacy Department for NGR-hTNF dilution); Patients may have had prior therapy providing the following conditions are met: - Chemotherapy and radiotherapy: wash-out period of 28 days - Surgery: wash-out period of 14 days Normal cardiac function and absence of uncontrolled hypertension; Written informed consent to participate in the study.
Test product, dose and mode of administration, batch number:	NGR-hTNF, 0.8 μg/m², 60 minutes iv infusion, every 3 weeks or weekly. Batch numbers: 06107, 07114, 08022
Duration of treatment:	Related to the clinical outcome (documented by modified RECIST for Malignant Pleural Mesothelioma)
Reference therapy, dose and mode of administration, batch number:	Not Applicable

Synopsis of Study Report

Company: Name of Finished Product: Name of Active Substance(s):	Tabular Format Referring to part of the Dossier Volume: Page:	(For National Authority Use only)

Criteria for evaluation (activity and safety):	Antitumor activity parameters: Antitumor activity was evaluated adopting standard imaging techniques and clinical assessment when applicable. Safety parameters: The safety was established by clinical and laboratory assessment according to NCI-CTC criteria version 3.0. The adverse events not listed on the NCI CTC grading system were graded on a five points scale and reported in detail on the CRF.
Statistical Methods:	The sample size was calculated using Simon's two-stage design method. The method provides the number of patients to enrol in the first (16) and second stage (11) of the study. An additional cohort of 12 patients will be subsequently enrolled and treated with a weekly schedule of NGR-hTNF. This cohort will be analyzed and the results will be reported separately from the previous patient population of 27 patients. If ≤1 of first 6 patients enrolled in this new cohort experience any grade 4 hematologic or grade 3–4 non-haematological toxicity during the first three weeks with the exclusion of nausea, vomiting, and fever that can be rapidly controlled with appropriate measures, 6 additional patients will be enrolled to test the feasibility of this weekly schedule on a larger cohort. Globally, this schedule will be considered safe if ≤2 of 12 patients experience any grade 4 hematologic or grade 3–4 non-haematological toxicity.

Synopsis of Study Report

Company: Name of Finished Product: Name of Active Substance(s):	Tabular Format Referring to part of the Dossier Volume: Page:	(For National Authority Use only)

Conclusions:	The evaluation denotes the following main findings: ➢ 71 and 41 NGR-hTNF-related adverse events were reported in the triweekly cohort and weekly cohort, respectively. These adverse events were generally of mild or moderate intensity. ➢ 27 patients in the triweekly cohort and 12 patients in the weekly cohort experienced grade 1-2 chills that promptly resolved spontaneously or with the administration of paracetamol. ➢ Only one drug-related severe presyncope was reported in a patient treated with the triweekly schedule, promptly resolved with appropriate medication. ➢ Overall study results included a disease control rate of 46%, which was maintained for a median progression-free time of 4.7 months, a median PSF of 2.8 months, and a median survival of 12.1 months. Only one patient achieved a partial response. ➢ In the weekly cohort a prolonged median PSF time in patients with disease control (9.1 months) was observed.