TECHNICAL SUMMARY OF RESULTS
2006-000756-41 [DEB-EPIV-201]

Sponsor: Debiopharm International SA	Tabulated Study Report		(For National Authority Use Only)
Name of Finished Product: Depelestat			
Name of Active Ingredient: Depelestat	Page:	Number:	

Title of study	Phase IIa multicenter 1 week treatment, randomised, double-blind, placebo controlled study of depelestat in patients suffering from acute respiratory distress syndrome [2006-000756-41; DEB-EPIV-201]
Study centers	**Centre #01**: Service de réanimation médicale, Hôpital Henri Mondor, 8 rue du Général Sarrail, 94010 Créteil cedex, France **Centre #02**: Service de réanimation médicale, Hôpital Saint-Louis, 1 avenue Claude Vellefaux, 75010 Paris, France **Centre #03**: Service de réanimation médicale A, Hôpital Pellegrin-Tripode, CHU Bordeaux, Place Amélie Raba-Léon, 33076 Bordeaux, France **Centre #04**: Service de réanimation médicale, Hôpital Cochin, 27 rue du Faubourg St-Jacques, 75679 Paris cedex 14, France **Centre #05**: Service de réanimation médicale, Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75908 Paris cedex 15, France **Centre #06**: Réanimation Médicale et Assistance Respiratoire, Hôpital Croix Rousse, 103 grande rue de la Croix-Rousse, 69004 Lyon, France **Centre #07**: Département d'Anesthésie Réanimation B (DAR B), Hôpital Saint Eloi, CHU Montpellier, 80 avenue Augustin Fliche, 34295 Montpellier cedex 05, France **Centre #08**: Réanimation médicale et médecine hyperbare, CHU d'Angers, 4 rue Larrey, 49933 Angers cedex 9, France **Centre #09**: Réanimation médicale, CHU Charles Nicolle, RDC Aile Est, Pavillon Félix Dévé, 1 rue de Germont, 76031 Rouen cedex, France **Centre #10**: Service de réanimation médicale, Hôpital Edouard Herriot, Place d'Arsonval, 69437 Lyon cedex 03, France **Centre #11**: Service des soins intensifs, UCL Saint-Luc, Avenue Hippocrate 10, 1200 Bruxelles, Belgium **Centre #12**: Intensive care unit, Erasme Hospital, Route de Lennik 808, 1070 Bruxelles, Belgium **Centre #13**: Réanimation Polyvalente, Centre Hospitalo-Universitaire Fattouma Burghuiba, rue du 1er juin, 5000 Monastir, Tunisia **Centre #14**: Intensive care unit, Policlinico Universitario A. Gemelli, Università Cattolica del Sacro Cuore, Largo A. Gemelli 8, 00168 Roma, Italy **Centre #15**: Servicio de Medicina Intensiva, Hospital de la Santa Creu i Sant Pau, Pavelló Sant Salvador, Av. Sant Antoni MaClaret 167, 08025 Barcelona, Spain **Centre #16**: Service de Réanimation Médicale Soins Intensifs d'urgence, CHU Grenoble, Hôpital Albert Michallon, Boulevard de la Chantourne, 38700 La Tronche, France **Centre #17**: Réanimation Chirurgicale Polyvalente du Dr Rouby, Groupe Hospitalier Pitié-Salpétrière, 47 Boulevard de l'Hôpital, 75013 Paris, France **Centre #18**: Réanimation Polyvalente, Groupe Hospitalier Intercommunal Toulon, Hôpital Font Pré, 1208 Avenue du Colonel Picot, 83100 Toulon, France
Publication	Not applicable
Clinical phase	IIa

Study dates	First patient in: 09 July 2006; Last patient out: 30 July 2007
Objectives	Primary • To assess the safety of Depelestat, a highly potent and specific inhibitor of human neutrophil elastase (hNE), administered by IV route in critically ill patients who were suffering from persistent acute respiratory distress syndrome (ARDS) • To assess efficacy of Depelestat on prevention and treatment of alveolar inflammation by measuring relevant biological parameters in blood and BAL of ARDS patients • To assess efficacy of Depelestat on prevention of early pulmonary fibrosis in ARDS patients, by assaying biological markers of lung collagen turnover in BAL and by measuring static compliance of the respiratory system. Secondary • To assess the effect of Depelestat on the evolution of the clinical status of ARDS patients : o oxygenation by measuring PaO2/FIO2 ratio o multi-organ dysfunction o ventilation-free days o mortality • To assess basic pharmacokinetics in ARDS patients
Methodology	This was a multicenter, randomised, double-blind, parallel groups, placebo-controlled, 1-week treatment of Depelestat, in patients who were suffering from persistent ARDS. The study periods consisted of a: • pre-treatment period as short as possible with a maximum of 48 hours since ARDS criteria are met • treatment period by Depelestat or placebo during 7 days, or until extubation of the patient • post-treatment period for 28 days after the diagnostic of ARDS, or until death whichever occurred first
Number of patients	Planned: 80; Enrolled: 84; Safety/ITT: 84 PP: 82; Completed: 23; Static compliance subset: 59; PK subset: 16
Diagnosis and main criteria for inclusion	Diagnosis: Acute Respiratory Distress Syndrome (ARDS) Patients with persistent ARDS, with a predicted body weight ≤ 90 Kg, whose legally authorised relative has signed an informed consent form.
Test product	Powder for solution of Depelestat at the concentration of 3 mg/mL at a dose of 1 mg/kg, for infusion.
Duration of treatment	The patients received treatment by Depelestat or placebo during 7 days or until extubation of the patient if this occurred before 7 days of treatment.
Criteria for evaluation	**Safety** *Clinical* • Incidence of adverse events (AE) • Change of vital signs • Incidence of nosocomial infections • Incidence of barotraumatisms (pneumothorax), during the period of mechanical ventilation • Evolution of organs failure assessed by global and specific Sequential Organ Failure Assessment (SOFA) scores

Criteria for evaluation (cont.)	*Biological* • Biochemistry and hematology including coagulation parameters • Microbiological cultures • Anti-Depelestat antibodies plasma levels at pre-treatment, post-treatment, and on Day 28, or at Intensive Care Unit (ICU) discharge **Efficacy** • Static compliance of the respiratory system • Assay of Positive end expiratory pressure (PCP III) concentration in blood and Bronchoalveolar lavage (BAL) fluid • Assay of cytokines and Hepatic Growth Factor (HGF) concentration in blood and BAL fluid • Assay of proteases [Matrix Metalloproteinase 2 (MMP2), elastase activity and anti-elastase capacity] in BAL fluid • Change of Partial arterial Oxygen pressure/Fraction of Inspired Oxygen (PaO2/FIO2) ratio • Organ failure assessed by SOFA score • Ventilator free days during the study period from Day 1 to Day 28 • 28 day, 60 day and 90 day all-cause mortality **Pharmacokinetics (PK)** PK plasma profile of Depelestat was assessed by the following parameters: • Non-compartmental analysis: o first administration: C0h, Cmax, tmax, and AUC0-8h; o last administration: C0h, Cmax, tmax, Css av, AUC0-8h, AUC0-t, AUC0-∞, λz, t½, AUMC0-8h, MRT, CL, Vss, Vz, accumulation ratio and FI. • Compartmental analysis: o Cmax, AUC, t1/2α, t1/2β, Vss, V1, CL, and CLd1
Statistical methods	The null hypothesis (H0) was that there was no difference between the study treatments and the alternative hypothesis (Ha) was that there was a true difference. Unless otherwise stated, the α risk p-values reported was two-sided and the statistical significance nominal limit was set to 0.05. For pharmacokinetic analyses, the α risk two-sided nominal limit was set to 0.10 to report the usual 90% two-sided confidence intervals (CIs). No adjustment was made for multiple comparisons due to the exploratory nature of this study. The safety analyses were performed only on the Safety population. The efficacy analyses were performed on each of the ITT and PP populations (ITT analysis was the primary analysis). The static compliance analyses were also performed on the static compliance subset. The pharmacokinetic analysis was performed on the PK subset population. The primary efficacy criteria were the static compliance last on-treatment and the relative change from pre-treatment to last on-treatment, both measured under Positive end expiratory pressure (PEEP) on the inflation curve. These efficacy criteria were both compared between treatment groups using Mann-Whitney test. The secondary efficacy criteria are listed below: • Static compliance measured on the deflation curve under PEEP change from pre-treatment to last on-treatment was compared between treatment groups • Hysteresis (area between the 2 inspiratory curves [Pressure/Volume (PV) tool 2 at 15 and 25 cmH2O)] was derived for each study group • Alveolar recruitment was evaluated for each study group • Kaplan-Meier survival curves were constructed for each treatment group to assess 28 day, 60 day and 90 day all-cause mortality. The log-rank test was used to compare all-cause mortality between treatment groups.

Statistical methods (cont.)	• Absolute changes from pre-treatment to during treatment and from pre-treatment to post-treatment were derived and compared between treatment groups, using either Anova or Mann-Whitney test, for the following secondary efficacy criteria: o PCP III concentration in BAL fluid and plasma o Alveolar neutrophil influx in BAL fluid o Cytokines and HGF concentration in BAL fluid and plasma • Changes in PaO2/FIO2 ratio from pre-treatment to during treatment and from pre-treatment to post-treatment were compared between treatment groups using Mann-Whitney test. • Evolution of organ failure assessed by global and specific change in SOFA scores from pre-treatment to during treatment, from pre-treatment to post-treatment, and from pre-treatment to Day 28 or ICU discharge were compared between treatment groups using Mann-Whitney test. • The number of ventilator-free days and the number of days under mechanical ventilation were compared between treatment groups using Mann-Whitney test. Frequency of adverse events frequencies was summarized by System Organ Class and Preferred Term, for both treatment period and post-treatment period. They were also tabulated by System Organ Class, along with severity grade and relationship to treatment. Laboratory parameters at pre-treatment, on-treatment, post-treatment and corresponding changes from pre-treatment were presented as descriptive statistics. Changes from pre-treatment to last on-treatment were compared between study groups by Anova or Cochran-Mantel-Haenszel test. Scatter plots showing pre-treatment versus on-treatment values and shift tables of pre-treatment versus worst-case on-treatment were provided. Vital signs at pre-treatment, on-treatment, post-treatment and corresponding changes from pre-treatment were presented as descriptive statistics. Changes from pre-treatment to last on-treatment were compared between study groups by Anova. Scatter plots showing pre-treatment versus worst-case and shift tables of pre-treatment versus worst-case on-treatment were provided. The PK analyses were performed on the PK subset population. Individual PK metrics were computed for Depelestat levels according to non-compartmental analysis. Descriptive statistics were presented for plasma concentrations at each time point (n, arithmetic mean, median, standard deviation [SD], minimum, maximum, coefficient of variation, and 90% confidence interval [90% CI]) and for all PK metrics (n, arithmetic mean, median, SD, minimum, maximum, coefficient of variation, 90% CI, geometric mean, geometric coefficient of variation; non parametric 90% CI for tmax) before and after the first and last study drug administrations, overall and per gender. PK metrics were compared between genders by an analysis of variance (ANOVA). A compartmental PK analysis was also performed, according to standard PK analysis methods and based on previous modelling data in healthy volunteers from study DEB-EPIV-101.
Summary and conclusions	After 7 days of treatment, no difference was observed in terms of static compliance between placebo and Depelestat groups. Kaplan-Meier survival curves were constructed for each treatment group to assess 28 day, 60 day and 90 day all-cause mortality. Results of the comparison of survival curves between the two study groups indicate no significant difference between the study groups: patients treated with Depelestat did not live significantly longer than those treated with placebo, in either ITT or PP populations. Kaplan-Meier survival curves were also constructed for each treatment group to assess 28 day, 60 day and 90 day all-cause mortality in the two classes of static compliance at baseline (< 30 mL/cmH2O and ≥ 30 mL/cmH2O), for the 79 patients that were alive during the first 3 days. Among the 22 patients that had a static compliance at baseline < 30 mL/cmH2O (11 patients in each group), 6 patients (54.6%) died in the placebo group and only 2 patients (18.2%) in the Depelestat group. Even if not statistically significant, the difference between study groups is observable at larger survival times (during the follow-up) for severe patients (< 30 mL/cmH2O at baseline). For IL-6 cytokine concentrations in BAL fluid, there was a statistically significant difference between Depelestat and placebo regarding the absolute change from pre-treatment to

Summary and conclusions (cont.)	post-treatment. However, mean IL-6 concentration at pre-treatment is higher in the Depelestat group than in the placebo group. This difference between study treatments in concentrations of IL-6 at pre-treatment is statistically significant and a slight but statistically significant correlation was observed between pre-treatment values and absolute change from pre-treatment to post-treatment. The number of patients that had an increase in IL-6 concentrations in BAL fluid was compared to the number of patients who had a decrease in IL-6 concentrations from pre-treatment to post-treatment, according to the treatment received. In the Depelestat group, only one patient had an increase in IL-6 concentrations in BAL fluid from pre-treatment to post-treatment, versus 11 patients in the placebo group. In the Depelestat group, 14 patients had a decrease in IL-6 concentrations versus 9 patients in the placebo group. The decrease/increase of IL-6 concentrations was statistically dependent on the study treatment. PCP III concentration change from pre-treatment to post-treatment did not show statistically significant difference between placebo and Depelestat, in BAL fluid nor in plasma, in both ITT and PP populations. No difference was observed between study groups in all other secondary efficacy criteria. Pharmacokinetic analyses were carried out in 16 patients. A slight Depelestat accumulation was observed after 7 days of treatment. On average, pharmacokinetic parameters from non-compartmental and compartmental analyses were similar in healthy subjects* and in patients with acute respiratory distress syndrome. No significant gender effect on the PK could be evidenced. Overall, 63 patients (75%) out of the 84 patients in the Safety population reported a total of 164 adverse events (treatment emergent adverse events and adverse events during post-treatment period). Incidence of treatment emergent adverse events was 55% of patients in the placebo group vs. 64% in the Depelestat group. No treatment emergent adverse event (TEAE) was related to the study drug. Incidence of adverse events during post-treatment period was 45% of patients in the placebo group vs. 57% in the Depelestat group. No AE during post-treatment period was related to the study drug. The most frequent AEs were anaemia (in 10.7% of the patients during treatment period), and nosocomial infection (in 15.5% of the patients during treatment period and in 27.4% of patients during post-treatment period). Eighteen (18) serious TEAEs were experienced during the treatment period by 14 patients (16.7%). Six (6) of them were fatal (2 in the placebo group and 4 in the Depelestat group). During the post-treatment period, 23 serious AEs were experienced by 19 patients (22.6%). Fifteen (15) of them were fatal (9 in the placebo group and 6 in the Depelestat group). There were no substantial changes in the laboratory parameters or vital signs from pre-treatment to on-treatment. _____ *Debiopharm (2007). "Phase I escalating single and one week repeated doses study of Depelestat by IV infusion in healthy volunteers". Clinical study report n° DEB-EPIV-101 (SGS Life Science Services n° B105562), May 2007.
GCP Statement:	This study was conducted under ICH E6 Good Clinical Practice, which has its foundation in the Declaration of Helsinki.
Amendments:	A protocol amendment was issued on 20 December 2006 to relax the inclusion/exclusion criteria slightly to facilitate recruitment without changing the risk to patients. Other changes in conduct of the study included: • values of vital signs only recorded at fixed time points • changes in analysis plans for some secondary and exploratory endpoints
Report Date	October, 2008