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## Abstracts

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PHASE I STUDIES WITH A NEW HUMAN NEUTROPHIL ELASTASE INHIBITOR, EPI-hNE4, ADMINISTERED BY INHALATION IN HEALTHY VOLUNTEERS C. Dubray<sup>(1)</sup>; F. Saudubray<sup>(2)</sup>; H. Clavien<sup>(2)</sup>; A. Bokman<sup>(2)</sup>; C. Lafuma<sup>(3)</sup>; A. Poncin<sup>(4)</sup>; S. Hiran<sup>(5)</sup>; A. Labbé<sup>(6)</sup>; <sup>(1)</sup>Laboratoire de Pharmacologie Médicale, BP 38 – 63001 Clermont-Ferrand (France); <sup>(2)</sup>DEBIOPHARM S.A. CH-1003 Lausanne (Switzerland); <sup>(3)</sup>INSERM Unité 492 – 94010 Créteil (France); <sup>(4)</sup>EUROGENTEC S.A. – 4102 Seraing (Belgium) <sup>(5)</sup>DYAX Corp Cambridge MA 02139 (USA) <sup>(6)</sup>Département de Pédiatrie, C.H.U.- 63009 Clermont-Ferrand (France);

OBJECTIVES: Phase I studies were designed to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamic effects of EPI-hNE4 (56 AA), a highly specific and potent inhibitor of human neutrophil elastase. BACKGROUND: In cystic fibrosis (CF), the balance between proteinases and their inhibitors may become severely disturbed. In these patients, activated PMN's are the most important source of elastase (hNE) which is considered as a key element in the lung damage. METHODS: Two placebo-controlled trials were conducted in 50 healthy male volunteers. In a first study, 8 escalating single doses were administered by inhalation in 38 subjects. The duration of aerosol administration ranged from 1 to 120 minutes, corresponding to estimated inhaled doses of 0.75; 1.5; 3.75; 7.5; 15; 22.5; 36 and 72 mg of EPI-hNE4, respectively. In a second repeated dose study, estimated inhaled doses of 3.75 mg and 15 mg were administered daily for 14 days in 12 healthy volunteers. In each study, a bronchoalveolar lavage (BAL) was carried out before and after single or repeated inhalations. RESULTS: EPI-hNE4 was perfectly well tolerated. No significant changes in routine laboratory, in vital signs as well as in pulmonary function tests occurred. After EPI-hNE4 inhalation, BAL showed increased antielastase capacity, significantly correlated with EPI-hNE4 levels and no change in bronchoalveolar cytology. A dose-dependent pharmacokinetic profile in the blood was observed after single inhalation. CONCLUSIONS: These studies showed that EPI-hNE4 effectively increases antielastase capacity, is safe and well tolerated. Initiation of phase 2 trials is warranted. This abstract is funded by: DEBIOPHARM S.A.