# TECHNICAL SUMMARY OF RESULTS
# 2004-002341-12 [DEB-EPI-206]

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

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| Title of study | Multicentre, 8-week, randomised, double-blind, placebo-controlled study of two doses of Depelestat in cystic fibrosis patients (2004-002341-12 [DEB-EPI-206]) |
| Study centres | **Centre # 01**: Zentrum fur Kinderheilkunde, Universitatsklinikum Essen, Hufelandstr. 55, D - 45122 Essen, Germany<br>**Centre # 02**: Mukoviszidose-Zentrum Köln, Mukoviszidose-Ambulanz, Klinik und Poliklinik für Kinderheilkunde der Universität zu Köln Joseph-Stelzmann Straße 9 - D - 50924 Köln, Germany<br>**Centre # 03**: Seacroft Hospital, Regional Adult CF Unit York Road, Leeds, West Yorkshire, LS14 6UH, England<br>**Centre # 04**: Papworth Hospital, Adult Cystic Fibrosis Centre, Dr. Diana Bilton,Papworth Everard Cambridge CB3 8RE, England<br>**Centre # 05**: Ospedale Civile Maggiore, Cystic Fibrosis Center, Piazzale Stefani, 1, 37126 Verona, Italy<br>**Centre # 07**: Hospital Ramón y Cajal, Departamento de Fibrosis Quística, Km 9.10028034 Madrid, Spain<br>**Centre # 08** and **#15**: Hospital Vall d'Hebron, Paseo Vall d'Hebron 119-129, 0835 Barcelona, Spain<br>**Centre # 09**: Paediatric Hospital, 1 G. Sofiiski, BG-1431 Sofia, Bulgaria<br>**Centre # 10**: Hospital "12 Octubre", Hospital Materno Infantil, Departamento de Fibrosis Quística 6a planta, Avda de Córdoba s/n, E – 28041 Madrid, Spain<br>**Centre # 11**: Belfast City Hospital, Adult CF Unit, Lisburn road, Belfast BT9 7AB<br>**Centre # 12**: University Hospital Gasthuisberg, Department of Respiratory MedicineKatholieke Universiteit Leuven, 49 Herestraat, B- 3000 Leuven, Belgium<br>**Centre # 16**: Ospidale. M. Bufalini, Divisione Pediatria e Patologia Neonatale, Centro di Fibrosi Cistica, USSL 39, Viale Ghiotti, 286 47023 Cesena, Italy<br>**Centre # 17**: Universitäts-Kinderklinik, Hoppe-Seyler-Str.1, 72076 Tübingen, Germany |
| Clinical phase | IIb |
| Study dates | First patient first visit: 25 January 2005; Last patient last visit: 04 January 2006 |
| Objectives | Primary Objective<br>To assess the safety of Depelestat at two different doses in cystic fibrosis (CF) patients with moderate pulmonary disease, particularly regarding the pulmonary function test (PFT) evolution on treatment, compared to placebo.<br>Secondary Objective<br>To compare two doses of Depelestat in terms of pharmacodynamics, by measuring change in human neutrophil elastase (hNE) activity in sputum during the treatment period and the post treatment period by comparison with the pre-treatment period. |

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| Methodology | In case of premature discontinuation, reason for discontinuation was recorded on the case report form (CRF). Every effort was made to follow up patients who discontinued prematurely in order to determine final outcome. Therefore, examinations normally scheduled at Visit 4 Day 57 were performed at a "premature discontinuation visit" conducted if possible the day after premature discontinuation. The date of premature discontinuation was defined as the date the decision was made to discontinue the patient, exception made of cases lost to follow-up (date of last news).<br>In case of premature discontinuation unrelated to treatment, the patient was replaced to obtain 21 complete CRFs per group for analysis.<br>In case of premature discontinuation due to a drug-related adverse event (AE), the Investigator immediately informed the Sponsor to discuss the patient's possible continuation in the study. If discontinuation was confirmed, the patient was not replaced.<br>Acute pulmonary exacerbation (APE)<br>If an APE (according to the definition of Fuchs) requiring intraveneous (IV) antibiotics occurred during the study, the patient continued treatment after the Investigator had carefully considered the functional tolerability of nebulisations and their acceptance by the patient during the acute episode.<br>If nebulisations seemed temporarily unacceptable, treatment was stopped during the period of exacerbation and resumed at its end, with the agreement of both the Investigator and the patient. In case of non-agreement, the patient was discontinued after discussion with the Sponsor.<br>At the end of the trial, PFT analysis was performed in 2 ways, with and without values from patients having experienced acute exacerbation during the study. |
| Number of patients | Planned 63 Enrolled 68 Safety 68<br>Safety-PFT 54 Intent-to-Treat (ITT) 66 Per-protocol (PP) 59 |
| Diagnosis and main criteria for inclusion | Patients aged > 6 years suffering from moderate and stable cystic fibrosis |
| Test product | Depelestat solution for inhalation 5.65 mg/3ml and 11.3 mg/3ml |
| Duration of treatment | 8 weeks |
| Criteria for evaluation | **Primary safety endpoint**<br>Forced expiratory volume (FEV) 1% predicted relative change from baseline to Day 57.<br>**Secondary safety endpoints**<br>• Incidence of AEs<br>• Change in vital signs (heart rate [HR], respiratory rate [RR], blood pressure [BP])<br>• FEV1 % predicted relative change from baseline to Day 15, 29, and 64<br>• Other PFT parameters (forced vital capacity [FVC], forced expiratory flow [FEF] 25-75) % predicted relative change from baseline to Days 15, 29, 57 and 64<br>• Change in safety blood chemistry and haematology from pre- to end of treatment<br>**Secondary efficacy endpoints**<br>• Change in sputum hNE activity from baseline to pre-nebulisation on Days 29, and 57<br>• Change in sputum hNE activity, from baseline to post-nebulisation on Days 1, 29, and 57 |

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| Criteria for evaluation (cont.) | • Change in sputum hNE activity between pre-nebulisation and post-nebulisation on Days 1, 29, and 57<br>• Change in sputum hNE activity from baseline to post-treatment on Day 64<br>• Response rate of Depelestat by dose. |
| Statistical methods | The safety analysis was conducted in the safety population. The efficacy (pharmacodynamic) and pharmacokinetic analyses were conducted in the ITT and in the PP populations. In addition, the PFT endpoints were analysed in the Safety-PFT population.<br>FEV 1% predicted relative change from baseline to on- and post-treatment was analysed by the mixed-effects model, with the treatment factor, and the randomisation factor (centre) as covariate. FEF25-75 and FVC were analysed in the same way.<br>Another analysis by the mixed-effects model was performed to explore the contribution of the treatment effect among factors that may influence the outcome of the patients. In this analysis, known predictive factors were added to the model, such as but not limited to age-group (6-15 years; > 15 years), FEV 1% predicted at baseline (FEF25-75, FVC respectively), or other pre-treatment variables.<br>Shift tables were constructed to assess PFT change between baseline and last on-treatment level.<br>Change in sputum hNE activity was analysed between treatment groups by the mixed-effects model.<br>Each Depelestat concentration measure was compared between treatments groups by the mixed-effects model. The change from baseline in sputum hNE activity was plotted against the corresponding Depelestat levels pooled for both active treatment groups. This relationship was explored by models available in WinNonlin to assess half maximal effective concentration ($EC_{50}$) and maximum efficacy ($E_{max}$) if data permitted. The mean change in sputum hNE activity per dose level was also plotted versus corresponding mean Depelestat levels.<br>Safety data were analysed on the adverse events incidence by the chi- square test or by Fisher exact test when expected cell frequencies were < 5. Laboratory parameters and vital signs were evaluated by the analysis of variance for continuous variables, and by chi-square or Fisher test for categorical variables. Shift tables and scatter plots were produced. |
| Summary and conclusions | **Regarding PFT analysis:**<br>The CF Phase IIb results showed a moderate decrease of PFT values, expressed as relative change of predicted FEV1, by 6.66% and 6.72% in the Depelestat low dose group (5.65 mg) and high dose group (11.3 mg) respectively. The absolute change was lower, by 4.18% and 4.17% respectively. The change from baseline to end of treatment was statistically different between Depelestat groups and placebo, as a mean relative increase for FEV1 was observed in the Placebo group (2.74%). No dose effect was observed in the Depelestat groups, also the high dose was the double of the low dose. A very slight decrease of FVC, expressed as relative change predicted values, was observed in Depelestat groups (0.77% and 3.12% for the low dose group (5.65 mg) and high dose group (11.3 mg) respectively). Despite the slight increase observed in the placebo group (2.74%), the change from baseline to end of treatment was not statistically different between Depelestat groups and placebo.<br>The placebo effect was higher than expected and led to a statistically significant difference on FEV1. Overall, the observed decrease of PFT values is weak and suggests a mild obstructive syndrome.<br>**Regarding pharmacodynamic effects :**<br>The results showed a mean decrease of elastase level after 2 months compared to baseline by 46 µg/mL with Depelestat 5.65 mg treatment versus 6 µg/mL with placebo. |

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| Summary and conclusions (cont.) | Concerning short term response in each patient assessing elastase inhibition after nebulisation by comparison with before, around 80% of patients receiving Depelestat were considered as responders, including 30% of complete responders in the high dose group.<br>These results confirm that Depelestat inhibits elastase activity in sputum of CF patients.<br>**Safety:**<br>Overall, Depelestat was well tolerated at both dose levels. Incidence of AEs was evenly distributed between the two Depelestat groups: 80% of patients reported AEs in the Depelestat 5.65 mg group vs. 74% in the Depelestat 11.3 mg group. In the placebo group, the incidence was 55%. Most AEs were mild to moderate in intensity and not related to the study drug.<br>Finally, no relevant elements were observed in both vital signs and/ or safety laboratory parameters. |
| GCP Statement | This study was performed in compliance with ICH E6 Good Clinical Practices, having its foundations in the Declaration of Helsinki. |
| Amendments | A protocol amendment was issued on 11 February 2005 upon request of the German National Health Authorities (Bundesinstitut für Arzneimittel und Medizinprodukte - BfArM). The inclusion and non-inclusion criteria, as well as the study discontinuation criteria were amended to conform with the drug legislation (Arzneimittelgesetz -Amg). |
| Report Date | 28 March 2007 |