1. SYNOPSIS

<table>
<thead>
<tr>
<th>Solvay Pharmaceuticals</th>
<th>Individual Study Table</th>
<th>(For National Authority Use only)</th>
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<tbody>
<tr>
<td>Name of Finished Product: Creon® 10 000 Minimicrospheres™</td>
<td>Referring to Part of the Dossier</td>
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<td>Name of Active Ingredient: Pancreatin</td>
<td>Volume:</td>
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**Title of Study:**
Open, randomized, crossover, multicenter study to investigate relative patient preference for Creon® 10 000 Minimicrospheres™ versus Creon® 8 000 microspheres in patients with pancreatic exocrine insufficiency caused by cystic fibrosis.

**Objectives:**
To compare Creon® 10 000 Minimicrospheres™ (Creon® 10 000 MMS) with Creon® 8 000 microspheres (Creon 8000 ms) with respect to patient preference in patients with pancreatic exocrine insufficiency caused by cystic fibrosis on a lipase-for-lipase dosing basis. A secondary aim was to compare these two products with respect to the coefficient of fat absorption (CFA).

**Methodology:**
Open, randomized, crossover, multicenter study in patients with pancreatic exocrine insufficiency caused by cystic fibrosis.

**Number of patients (planned and analyzed):**
It was planned to randomise 86 patients so that 54 patients who were decided about their treatment preference would be included. Although not planned in the protocol, an interim analysis was performed after 31 patients had completed the study and revealed a highly significant preference for Creon® 10 000 MMS. It was considered unethical to continue with the study and hence the study was stopped prematurely after 60 patients were screened. Thus 59 patients were included, 57 analyzed for safety and clinical symptomatology and 54 for preference. 22 patients were included in the analysis for stool sample data.

**Diagnosis and main criteria for inclusion:**
Male or female patients, capable of swallowing capsules, with pancreatic exocrine insufficiency caused by cystic fibrosis requiring pancreatic enzyme replacement therapy.

**Test product, dose and mode of administration, batch number:**
During one of the crossover periods Creon® 10 000 MMS capsules (Batch Nos. 013 and 026) were administered orally during meals and fat-containing snacks. Dosage was calculated during the run-in period according to the previous dosage of pancreatic enzymes on a lipase basis. Lipase intake was stable throughout all study periods.
**Duration of treatment:**
Ten weeks (including run-in and cross-overs)

**Reference therapy, dose and mode of administration, batch number:**
During the run-in period Creon 8 000 ms capsules (Batch Nos. 198 and 203) were administered orally. Dosage was determined based on an equal number of lipase units as for the pancreatic enzyme therapy taken prior to the study. During one of the crossover periods Creon 8 000 ms capsules (Batch Nos. 198 and 203) with the same lipase content were administered. Study medication was taken during meals and fat-containing snacks.

**Criteria for evaluation:**

**Efficacy:**
Patient preference assessed on completion of both treatment periods, stool collection data, clinical symptomatology, clinical global impression of disease symptoms, patient diary.

**Safety:**
Adverse events and vital signs at each visit, and physical examination findings pre and post treatment.

**Statistical methods:**
Confirmatory analysis by means of a two-sided sign test for the primary parameter (patient preference) analysis of variance and analysis of covariance for stool collection data, and descriptive summaries for all parameters.
Summary – Conclusions

Efficacy and Preference Results:
Creon® 10 000 Minimicrospheres™ were preferred by 47 (87%) patients out of the 54 patients and Creon® 8 000 microspheres by 4 (7%) patients; 3 were undecided. This difference was statistically significant (p<0.0001).

Equivalence of the efficacy parameter CFA was proven for the two products: median is 94.4% for both treatments. The confidence interval for the difference Creon® 10 000 MMS – Creon 8 000 ms was included in the equivalence range of +/- 15% and therefore equivalence as stated in the protocol was proven statistically. No relevant differences were seen between the treatments for any of the other parameters.

Safety Results:
There were a total of 198 adverse events in a total of 58 patients. 32 patients had AEs in both treatment periods. Forty-six patients (83.6%) had adverse events for Creon 8 000 ms, and 48 patients (84.2%) for Creon® 10 000 MMS. The most frequent adverse events were cough, headache, lung disorder, and abdominal pain. There were 187 treatment emergent adverse events which occurred in 58 patients also.

There were eight serious adverse events leading to hospitalisation of patients; seven occurred during the Creon® 10 000 MMS treatment phase and one during the Creon 8000 ms treatment phase. The serious adverse events reported during Creon® 10 000 MMS were: exacerbation of a chest infection, intussusception, meconium ileus equivalent, chest infection, appendix abscess (withdrew from study), torsion of left testes and reinseration of gastrostomy tube. The serious adverse event reported during Creon 8000 ms was severe abdominal pain. All these serious adverse events were considered, according to the investigator’s opinion, as not related or unlikely to be related to study treatment.

Five patients in total withdrew during the study, one due to a serious adverse event and four due to non-serious adverse events. All the non-serious adverse events were abdominal pain: two occurred during the run-in period on Creon 8000 ms and two whilst on Creon® 10 000 MMS. All made complete recoveries.

Conclusions:
- Creon® 10 000 MMS was preferred to Creon 8000 ms by patients with pancreatic exocrine insufficiency caused by cystic fibrosis.
- The analysis of CFA proved equivalent efficacy of Creon® 10 000 MMS and Creon 8000 ms.
- Both treatments were considered to be safe and tolerable.
- Higher preference and acceptability for Creon® 10 000 MMS than for Creon 8000 ms was probably due to the smaller size of the capsules.
- The preference of patients for Creon® 10 000 MMS should have favourable implications for patient compliance.