2. SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Company:</th>
<th>Solvay Pharmaceuticals</th>
<th>Individual Study Table</th>
<th>(For National Authority Use Only)</th>
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</thead>
<tbody>
<tr>
<td>Name of Finished Product:</td>
<td>Creon® 25 000 Minimicrospheres™</td>
<td>Volume:</td>
<td></td>
</tr>
<tr>
<td>Name of Active Ingredients:</td>
<td>Pancreatin</td>
<td>Page: 1</td>
<td></td>
</tr>
</tbody>
</table>

**Title of Study:** Double-blind, bicenter, randomized, crossover study to prove equivalent efficacy and tolerance of Creon® 25 000 Minimicrospheres™ versus Creon® 25 000 Microspheres (Pankreon® forte) in patients with pancreatic exocrine insufficiency caused by cystic fibrosis.

**Investigator(s):** [Redacted for privacy reasons]

**Study center(s):** [Redacted for privacy reasons]

**Publication (reference):** not applicable

**Study period (years):** 29/2/96 - 12/5/97

**Phase of development:** 3

**Objective(s):** To prove equivalent efficacy and tolerability of Creon® 25 000 Minimicrospheres™ and Creon® 25 000 Microspheres (Pankreon® forte) on a lipase-per-lipase basis regarding fat absorption.

**Methodology:** Double-blind, bicenter, randomized crossover study in patients with pancreatic exocrine insufficiency caused by cystic fibrosis.

**Number of patients (planned and analyzed):** It was planned to have 32 evaluable patients. Actually, 34 patients were screened. 33 were included and 29 patients were analyzed for safety and efficacy. 28 patients were evaluable for the CFA. The study was stopped prematurely due to a too low recruitment rate.

**Diagnosis and main criteria for inclusion:** Male or female patients, 4 years of age or older, 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® 25 000 Minimicrosphere™ capsules (Batch No. 100R) were administered orally during meals and snacks. During one of the crossover periods Creon® 25 000 Microsphere capsules (Pankreon® forte, Batch No. 099R) were administered orally during meals and snacks. One third of the number of capsules administered during the run-in period was taken.

**Duration of treatment:** Two weeks.

**Reference therapy, dose and mode of administration, batch number:** During the run-in period Creon® 8 000 Microsphere capsules (Batch No. 679.01) were administered orally during meals and snacks. Dosage was determined based on an equal number of lipase units as for the pancreatic enzyme therapy taken prior to the study. During the run-in period the patients took 3 times as much Creon® 8 000 Microsphere capsules compared to Creon® 25 000.
SUMMARY - CONCLUSIONS

EFFICACY RESULTS: In the intent-to-treat analysis for the primary efficacy parameter CFA an equal mean absorption was found for Creon® 25000 Minimicrospheres™ (89.1% ± 7.3) as for Creon® 25000 Microspheres (86.7% ±12.5). The 90% confidence interval for the ratio Creon® 25000 Minimicrospheres™/Creon® 25000 Microspheres was [0.990 ; 1.085] and lay entirely in the equivalence range of [0.905 ; 1.105] as required in the protocol for the proof of equivalence (p = 0.012). In the per-protocol analysis this result was confirmed. In the analysis of the secondary efficacy parameters similar results for both treatments were seen.

SAFETY RESULTS: In total 10 patients (34.5 %) in both treatment groups suffered from 12 adverse events (TEAE) in each group, mainly abdominal pain, headache and infection. No major differences were seen regarding the frequency of adverse events between the two treatments. Most frequent adverse events were abdominal pain (8 patients = 27.6 % / Creon® 25000, 7 patients = 24.1% / Creon® 25000 Minimicrospheres™), headache: (3 patients = 10.3% / Creon® 25000, 2 patients = 6.9% / Creon® 25000 Minimicrospheres™) and infections (3 patients = 10.3 % in the Creon® 25000 Minimicrospheres™ group, none in the Creon® 25000 group). Two patients had serious adverse events (acute exacerbation of bronchitis), both during the run-in period with Creon® 8000 Microspheres. One additional patient was withdrawn due to adverse events (obstipation, stomach pain). This withdrawal occurred during the run-in period with Creon® 8000 Microspheres.

CONCLUSION: Creon® 25000 Minimicrospheres™ and Creon® 25000 Microspheres showed equivalent efficacy on the coefficient of fat absorption on a lipase per lipase basis, both in the intent-to-treat and per-protocol patient group. Both products were safe and well tolerated.