## 2. SYNOPSIS

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<thead>
<tr>
<th>Name of Company:</th>
<th>Individual Study Table</th>
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<td>Solvay Pharmaceuticals</td>
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**Name of Finished Product:**
Creon® 10,000

**Name of Active Ingredient:**
Pancreatin

**Volume:**

**Page:**

**Title of Study:**
Open-label, randomized, three-way, cross-over single-center study to prove the equivalence of a single dose of Creon® 10,000 Minimicrospheres™ and Pancrease® by using the ¹³C-mixed triglyceride breath test in patients with pancreatic exocrine insufficiency due to cystic fibrosis.

**Investigator(s):**
Removed for privacy reasons

**Study center(s):**
Removed for privacy reasons

**Publication (reference):**
None

**Study period:**
30/11/98 to 03/11/99

**Phase of development:**
IIlb

**Objectives:**
Primary: To demonstrate equivalent fat digestion of Creon® 10,000 Minimicrospheres™ compared to Pancrease® on a lipase per lipase basis using the ¹³C-mixed triglyceride breath test (MTG) in cystic fibrosis patients subject to a sensitivity test versus placebo and to assess the safety and tolerability of Creon® 10,000 Minimicrospheres™ as single administration of 2500 lipase units/g fat (MTG study).

Secondary: To establish the rate of gastric emptying in patients with cystic fibrosis and in healthy volunteers by using the ¹³C octanoic acid breath test (Gastric emptying [GE] study according to protocol Amendment 2).

**Methodology:**
Open-label, single-center, randomized, placebo-controlled, three-way cross-over study in 22 patients with cystic fibrosis followed by a non-randomized study in 12 cystic fibrosis patients and in 12 healthy volunteers (Protocol Amendment 2).

**Number of patients (planned and analyzed):**
Planned: 22 CF patients for the MTG study, 12 cystic fibrosis patients (from the MTG study) and 12 healthy volunteers for the GE study; entered and analyzed: 21 patients for the MTG study; 14 cystic fibrosis patients and 13 healthy volunteers for the GE study.
### Diagnosis and main criteria for inclusion:

**MTG study:**
Male or female patients aged 4-18 years with pancreatic exocrine insufficiency due to cystic fibrosis who were taking pancreatic enzyme replacement medication in a stable dose for at least half a year prior to study entry with satisfactory symptom control.

**GE study:**
Subjects who participated in the previous study S2453109 or in the MTG study who gave written informed consent to participation in the GE study. The patients were divided into two groups: positive response respectively negative response to the MTG test.

### Test product, dose and mode of administration, batch number:

**MTG study:**
Creon® 10,000 Minimicrospheres™ capsules, consisting of enteric-coated pancreatin pellets containing 150 mg pancreatin with declared enzyme values of 10,000 Ph. Eur. units of lipase, 8,000 Ph. Eur. units of amylase, and 600 Ph. Eur. units of protease. The batch number was 021U. The amount of study medication to be taken together with the test meal depended on the fat content of the test meal: 2 capsules with a fat content ≤10 g, 3 capsules with a fat content >10-12 g, or 4 capsules with a fat content >12-15 g.

**GE study:**
No study drug was administered during the GE study. The patients took their usual enzyme replacement therapy.

### Duration of treatment:

**MTG study:**
Three cross-over test days with a single administration of study drug. Subsequent test days were separated by a wash-out period of 3-8 days.

**GE study:**
Single test day without study drug.

### Reference therapy, dose and mode of administration, batch number:

1. **Pancrease®** capsules, containing 243 mg pancrelipase with declared enzyme values of >5,000 BP units of lipase, >3,000 BP units of amylase, and >3,350 BP units of protease. The batch number was 078G97B. The number of capsules to be taken together with the test meal depended on its fat content: 4 capsules with a fat content ≤10 g, 6 capsules with a fat content >10-12 g, or 8 capsules with a fat content >12-15 g.

2. **Placebo**
Placebo capsules matching Creon® 10,000 Minimicrospheres™ capsules (Batch number 020U). The amount of placebo capsules to be taken was the same as for Creon® 10,000 Minimicrospheres™ capsules.
### Criteria for evaluation:

**Efficacy:**
- Primary: Mean cumulative percentage of exhaled $^{13}$C over 6 hours.
- Secondary: Delta values, delta over baseline values.

**Safety:**
- Adverse events, physical examination findings, vital signs.

### Statistical methods:
- Analysis of variance (ANOVA) for cumulated expired tracer after six hours (MTG study).
- Standard descriptive statistics for both the main and the GE study.

### Summary – Conclusions

**Efficacy Results:**

**MTG study:**
After 6 hours, mean cumulated expired tracer was highest under Pancrease® treatment (12.201%), followed by Creon® 10,000 Minimicrospheres™ (8.419%) and placebo (6.454%). However, there was a high variability and for several patients the cumulated expired trace did not start to rise until the end of the 6-hour period. Due to this fact, the main efficacy analysis was not based on the logarithmic transformation but on the cumulated expired tracer itself. No superiority of Creon® 10,000 Minimicrospheres™ over placebo could be shown ($p=0.303$, ANOVA). Therefore, according to the protocol, the equivalence of Creon® 10,000 Minimicrospheres™ and Pancrease® was not further evaluated.

**GE study:**
The peak outcome of % dose per hour was higher for healthy volunteers than in both groups of cystic fibrosis patients. The response curve for cystic fibrosis patients had a similar shape but peak values were less pronounced. No major differences between subjects with a positive respectively negative response to the MTG could be identified in the $^{13}$C octanoate breath test with the exception of a slightly higher % dose/hour up to 2 hours in the patients with a positive response as compared to those with a negative response. Also, no major differences between the CF patients and the healthy controls were observed. Therefore, differences in gastric emptying in the CF patients were not the reason for the slow rise in expired tracer of the MTG test.
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### Safety Results:

#### MTG study:
Twelve patients (60.0%) reported at least one adverse event during treatment with placebo, 9 patients (45.0%) during treatment with Creon® 10,000 Minimicrospheres™, and also 9 patients (47.4%) during Pancrease® treatment. The most frequently reported AEs were abdominal pain (3 patients on placebo, 2 patients on Creon® 10,000 Minimicrospheres™, and 2 patients on Pancrease®), and diarrhea (2 patients on placebo, 2 patients on Creon® 10,000 Minimicrospheres™, and 1 patient on Pancrease®). One patient experienced a serious AE (dyspnea) two days after the last breath test (Pancrease®). Three patients (15.0%) had an AE that was considered at least possibly related to study drug during placebo treatment, 3 patients (15.0%) during treatment with Creon® 10,000 Minimicrospheres™ and 1 patient (5.3%) during Pancrease® treatment.

No major changes from baseline in vital signs and physical examination findings occurred during the MTG study.

#### GE study:
During the GE study, a total of 5 AEs were reported in 5 subjects (4 cystic fibrosis patients and 1 healthy volunteer).

### Conclusion:
- No superior efficacy of Creon® 10,000 Minimicrospheres™ over placebo could be shown with respect to cumulated expired tracer after 6 hours. Therefore, according to the protocol, the equivalence of Creon® 10,000 Minimicrospheres™ and Pancrease® was not further evaluated.
- Delayed gastric emptying did not explain the inconclusive results of the MTG test; therefore, this MTG test possibly did not work properly in this study.
- The safety and tolerability of a single dose of Creon® 10,000 in patients with pancreatic exocrine insufficiency due to cystic fibrosis was good and no relevant difference to placebo and Pancrease® was found.