2. SYNOPSIS

<table>
<thead>
<tr>
<th>Solvay Pharmaceuticals</th>
<th>Individual Study Table</th>
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</thead>
<tbody>
<tr>
<td>Name of Finished Product: Creon® 10 000 Minimicrospheres™</td>
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<tr>
<td>Name of Active Ingredient: Pancreatin</td>
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<tr>
<td>Title of Study: Double-blind, placebo-controlled, randomized, multicenter, crossover study to investigate whether the dose-dependent effect of Creon® Minimicrospheres™ on the postprandial fat assimilation can be shown with the $^{13}$C-mixed triglyceride breath test in patients with pancreatic exocrine insufficiency due to cystic fibrosis</td>
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**Investigator(s):**

Removed for privacy reasons

**Study center(s):**

Removed for privacy reasons

Publication (reference): Not applicable

Study period: 18 Sep 2000 - 22 Jan 2001

Objectives: To investigate whether the dose-dependent effect of Creon® MMS on the postprandial fat assimilation can be shown with the $^{13}$C-mixed triglyceride breath test in cystic fibrosis patients with pancreatic exocrine insufficiency

Methodology: 3 single doses of Creon® MMS on 3 days together with a $^{13}$C-mixed triglyceride breath test and a wash-out period of 3-7 days between each of the three tests

Number of patients (planned, screened, randomized and analyzed): 12 patients were planned: A total of 12 patients were randomized and these 12 patients were analyzed.

Diagnosis and main criteria for inclusion: Male or female patients, 4 years of age or older, with CF and PEI, satisfactory symptom control after pancreatic enzyme supplementation according to the medical history and the clinical experience of the investigator. Severe pancreatic exocrine insufficiency according to the medical history, the clinical symptomatology of the patient and the clinical experience of the investigator.

Test product, dose and mode of administration, batch number:
- Creon® Minimicrospheres™ capsules: batch No. 004W 5 000 FIP U lipase
- batch No. 005W 10 000 FIP U lipase

administered orally with some fluid. The dosage was four capsules per test meal (placebo or 5 000 lipase U or 15 000 lipase U or 40 000 lipase U).

Duration of treatment: 3 single doses of Creon® MMS on 3 days

Reference therapy, dose and mode of administration, batch number: Capsules with placebo (batch No. 047T) were administered orally with the same dosage as the test product.
### Criteria for evaluation:

**Efficacy:**
- Primary: mean cumulative percentage of exhaled $^{13}$CO$_2$ over 6 hours (% of dose administered) after a single intake of study medication.
- Secondary: expired tracer per hour, (% of dose per hour), delta values (%0) and delta over baseline (%0).

**Safety:**
- Adverse events, vital signs, physical examination findings, hematology, blood chemistry and urinalysis parameters.

### Statistical methods:

The analysis for the primary and secondary efficacy parameters was done using analysis of variance techniques with patient, treatment and period as fixed factors. Pairwise treatment contrasts were displayed, along with 95% confidence intervals.

Safety data were summarized for all patients using descriptive statistics and frequency tables.

### Summary - Conclusions

**Efficacy Results:**
- All dosages of Creon® MMS showed superior cumulative tracer recovery compared with placebo.
- The dose-dependent effect of Creon® MMS on postprandial fat assimilation could only be shown for the low dose versus the high dose. A full dose-dependency could not be demonstrated with this $^{13}$C-mixed triglyceride breath test.

**Safety Results:**
- In total, 7 patients (58.3%) suffered from adverse events at screening, 8 patients (88.9%) had adverse events when taking placebo and 11 patients (91.7%) when different doses of Creon® were given. No differences in treatment-emergent adverse events were detected between the three dosages of Creon® and placebo. No serious adverse events or deaths occurred. No patient withdrew due to adverse events. Neither laboratory parameters nor vital signs or physical examinations revealed any safety differences between Creon® and placebo.

**Conclusion:**
- Creon® Minimicrospheres™ is effective in the therapy of lipid maldigestion in cystic fibrosis patients with pancreatic exocrine insufficiency, as it was shown by the $^{13}$C-mixed triglyceride breath test.
- A dose-dependency could only be shown for the comparison low dose versus high dose of Creon® Minimicrospheres™.
- All single dosages of Creon® Minimicrospheres™ were safe and well tolerated.
- This $^{13}$C-mixed triglyceride breath test may be optimized to be sensitive enough to show dose-dependent effects of pancreatic enzyme supplementation.