### SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Company:</th>
<th>Individual Study Table Referring to Part of the Dossier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvay Pharmaceuticals</td>
<td>For National Authority Use Only</td>
</tr>
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<table>
<thead>
<tr>
<th>Name of Finished Product:</th>
<th>Volume:</th>
</tr>
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<tbody>
<tr>
<td>Creon® 25 000</td>
<td></td>
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<table>
<thead>
<tr>
<th>Name of Active Ingredients:</th>
<th>Page:</th>
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<tbody>
<tr>
<td>Creon® 25 000 minimicrospheres</td>
<td>1</td>
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</tbody>
</table>

**Title of Study:** Open single-center study to investigate the pharmacodynamics of Creon® 25 000 minimicrospheres measured by $^{13}$C-triglyceride breath test and gastric emptying measured by $^{13}$C-octanoate breath test in cystic fibrosis patients using healthy children not receiving Creon® 25 000 minimicrospheres as controls.

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

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


**Study period (years):** 09/08/95 to 22/11/95

**Phase of development:** 4

**Objective(s):** To determine the pharmacodynamics of Creon® 25 000 minimicrospheres measured by the $^{13}$C-triglyceride breath test in cystic fibrosis patients in comparison to healthy children not receiving Creon® 25 000, whereby the main efficacy parameter was the proportion of $^{13}$CO$_2$ in the expired air.

**Methodology:** Open, single-center, non-randomized study with healthy volunteers not receiving study medication as control.

**Number of patients (planned and analyzed):** It was planned to include 10 completely evaluable patients and 10 completely evaluable healthy volunteers. Actually, 11 patients and 11 volunteers entered the study of whom 10 in each group completed the study. All 11 patients and 11 volunteers were evaluable for the $^{13}$C-octanoate test and nine patients and ten volunteers were evaluable for the $^{13}$C-triglyceride test. Seven patients were male and four patients were female and had a mean age of 11.3 years (range 5 - 19 years). Of the volunteers four were male and seven female with a mean age of 10.5 years (range 5 - 20 years).

**Diagnosis and main criteria for Inclusion:** Male and female patients, 4 to 35 years of age, with proven cystic fibrosis (CF) who took pancreatic enzyme replacement therapy for at least half a year prior to entry into the study and healthy volunteers of the same age who did not take any concomitant medication.

**Test product, dose and mode of administration, batch number:** Creon® 25 000 minimicrosphere capsules (Batch No. 08, Lot No. 037V3), administered orally before each breath test prior to a standardized test meal to patients. Volunteers did not receive study medication.

**Duration of treatment:** Two single doses administered on Day 1 and Day 5 of the study.

**Reference therapy, dose and mode of administration, batch number:** not applicable

**Criteria for Evaluation:**
- **Efficacy:** Cumulated expired tracer in % of dose (primary variable for both breath tests).
- **Safety:** Adverse events, vital signs, physical examination findings.
SUMMARY - CONCLUSIONS

EFFICACY RESULTS: $^{13}$C-triglyceride breath test

Two analyses of the $^{13}$C triglyceride data have been done. One patient (No. 7) was not adequately treated with one single dose of Creon® 25 000. The primary analysis of the data was therefore done excluding this patient. For the $^{13}$C-triglyceride test mean cumulated expired tracer over time was somewhat higher in volunteers as compared to patients in the time frame of between 45 and 435 minutes and reached the same level thereafter indicating similar cumulative tracer recovery in patients treated with Creon® 25 000 minimicrospheres and in volunteers. Maximal delta over baseline, in the mean, was reached 85 minutes earlier in volunteers (258 minutes) than in patients (343 minutes). The same was applicable for the time of maximal increase of delta which was, in the mean, reached 142 minutes earlier in volunteers (107 minutes) than in patients (248 minutes). Mean maximal delta over baseline and mean maximal increase of delta were similar in both groups.

$^{13}$C-octanoate breath test

Mean course of cumulated expired tracer over time for the $^{13}$C-octanoate test was almost identical in both volunteers and cystic fibrosis patients. 95% confidence intervals for the difference between patients and volunteers were symmetrical around 0 indicating no difference between patients and volunteers. Mean increase of delta over baseline was higher in volunteers than in patients up to 280 minutes and similar in both groups thereafter. Delta over baseline reached its maximum in the mean after 187 minutes in patients (range 40 - 310 minutes) and somewhat earlier, i.e. after 171 minutes in volunteers (range 50 - 280 minutes).

SAFETY RESULTS:

During the course of this study a total of six adverse events in four patients were documented, four of which started after the first intake of study medication and two already at the pre-study assessment. All events were of mild intensity and none was considered by the investigator to be related to treatment with Creon® 25 000. Volunteers did not experience any adverse event.

For vital signs in both patients and volunteers no major changes between visits were observed.
CONCLUSIONS:

- No difference in cumulative recovery of $^{13}\text{C}$ in breath after ingestion of triglyceride tracer between patients and volunteers was seen.
- Enzyme substituted CF patients show no difference in gastric emptying time compared to healthy controls.
- In 9 of 10 CF patients a sufficient fat assimilation could be achieved by a single dose of 1 capsule Creon® 25 000 minimicrospheres.
- A single dose of 1 capsule Creon® 25 000 minimicrospheres was well tolerated.

Date of the report: November 3, 1997