**SYNOPSIS**

<table>
<thead>
<tr>
<th>Name of Sponsor/Company:</th>
<th>Solvay Pharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Finished Product:</td>
<td>Creon® for children</td>
</tr>
<tr>
<td>Name of Active Ingredient:</td>
<td>Pancreatin</td>
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</tbody>
</table>

**Title of Study:**
Open-label, single-arm, multicenter study to evaluate the efficacy and tolerability of Creon® for children in infants with pancreatic exocrine insufficiency caused by cystic fibrosis

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

**Study Center(s):**
The study was performed at two study centers in Italy

**Publication (Reference):**
Not applicable.

**Study Period:**
27 JUN 2002 (First Subject First Visit) – 7 SEP 2004 (Last Subject Last Visit)

**Phase of Development:**
Phase III

**Objectives:**
Major aim of the study was to evaluate the efficacy of Creon® for children in infants with pancreatic exocrine insufficiency due to cystic fibrosis. The primary efficacy parameter was the coefficient of fat absorption (CFA), secondary efficacy parameters were steatorrhea, fecal energy loss, stool characteristics, gastrointestinal symptoms, response (CFA above 90%), hematology and biochemistry parameters, nutritional parameters, and patient’s acceptance. Further aims were the investigation of the safety and tolerance of Creon® for children in this study population.

**Methodology:**
Open-label, single-arm study performed in two centers. During a baseline period of up to ten days, subjects were hospitalized and pancreatic exocrine insufficiency was assessed including a 72 h fat balance study (stool collection and dietary records) for the calculation of the CFA. Thereafter, a treatment period of eight weeks (total) was performed. At the end of the first two weeks of this treatment period, subjects were again hospitalized, a 72 h fat balance study was performed, and safety and secondary efficacy parameters were determined. Two further visits were performed after five and eight weeks of treatment during which safety and secondary efficacy parameters were determined, but no fat balance study was performed. Throughout the treatment period, the subjects’ parents kept a diary in which study medication intake, gastrointestinal symptoms, stool frequency and stool consistency were recorded. A clinical laboratory was performed at the first and the last visit.

**Number of Subjects (Planned, Consented, Randomized and Analyzed):**
The planned, consented, and treated number of subjects was 12. All 12 subjects were analyzed in the safety and intent-to-treat subject samples. The per-protocol subject sample comprised 10 subjects.
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<td><strong>Diagnosis and Main Criteria for Inclusion:</strong></td>
<td>Subjects of either sex, aged 1-24 months, with proven diagnosis of cystic fibrosis and pancreatic insufficiency and a CFA &lt; 70% were eligible to enter the study.</td>
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</table>
| **Test Product, Dose and Mode of Administration, Batch Number:** | Name: Creon® for children in minimicrospheres  
Dose: Individual, 2000 lipase units per g fat intake  
Route: Oral (minimicrospheres)  
Batch: 15601 |
| **Duration of Treatment:** | Eight weeks |
| **Reference Therapy, Dose and Mode of Administration, Batch Number:** | Not applicable |
| **Criteria for Evaluation:** | **Efficacy:**  
Primary: CFA  
Secondary: steatorrhea, fecal energy loss, stool characteristics, hematology and blood chemistry parameters, nutritional parameters, gastrointestinal symptoms, body height and weight, and subject’s acceptance of therapy  
**Safety:**  
Adverse events and vital signs |
| **Statistical Methods:** | Data were analyzed descriptively. The paired t-test was used for testing the intraindividual change from baseline. |
| **Summary – Conclusions** | **Efficacy Results:**  
For the ITT sample the primary efficacy parameter CFA significantly increased from a baseline mean of 58.0% to a mean of 84.7% after two weeks (mean increase 26.7%, 95% confidence interval [12.9%;40.4%], p=0.0013).  
After two weeks of treatment, four subjects (33%) were responders (CFA>90%). At baseline, all subjects had steatorrhea, and at after two weeks of treatment seven subjects (58%) had steatorrhea. Mean stool fat decreased by 7.98 g/day (from 13.26 to 5.28 g/day), the decrease being statistically significant (p=0.0013). Mean stool weight decreased by 30.3 g/day (from 109.6 to 79.3 g/day), and mean dietary fat intake increased by 2.25 g/day (from 32.02 to 34.27 g/day). No major changes were seen for hematological and biochemical parameters with the exception of increases of vitamins A and E. Height and weight increased, but the weight for height percentile remained nearly constant and close to 100%. Subject’s acceptance of therapy was very good for nine (75%, after two weeks of treatment) or 11 (92%, all other visits) of the subjects and was good or moderate for the other subjects. Gastrointestinal symptoms were very infrequent (only one subject at baseline).  
Results for the PP sample were similar to results for the ITT sample. |
On average, subjects were treated with a mean daily dose of 73677.4 lipase units. When expressed per kg body weight this was 8215.7 lipase units, and when expressed per g fat intake it was 2205.2 lipase units.

Safety Results:
No subject died, no serious adverse event was reported and no subject was withdrawn due to adverse events. Nine subjects (75%) experienced at least one treatment emergent adverse event (TEAE). The most frequent system organ classes (SOCs) were general disorders and administration site conditions, and infections and infestations (four subjects, 33%, each), and gastrointestinal disorders, and respiratory, thoracic and mediastinal disorders (three subjects, 25%, each). All other SOCs were reported for at most one subject. Preferred terms reported for more than two subjects were pyrexia (four subjects, 33%), and cough (three subjects, 25%). The only related TEAE was constipation, reported for one subject (8%). No TEAE was severe, and only one TEAE (gastroenteritis adenovirus) in one subject (8%) was moderate in intensity. All other TEAEs were mild.

Conclusion:
Creon® for children was efficacious regarding the improvement of the CFA, stool fat excretion, and fecal energy loss in infants with pancreatic exocrine insufficiency due to cystic fibrosis. The stool weight decreased while fat intake did not change. No relevant changes were observed for hematological and biochemical parameters. The height for weight percentile remained close to 100%. Subject acceptance was mostly very good.

The safety and tolerability of Creon® for children was good.