1. SUMMARY

TITLE

Double-blind, multicenter, crossover study comparing the efficacy and tolerance of Creon® 25 000 versus Panzytrat® in patients with pancreatic exocrine insufficiency caused by cystic fibrosis.

CHIEF INVESTIGATOR

INVESTIGATORS

Four children hospitals in Germany.

STUDY DESIGN AND PURPOSE

This trial was a double-blind crossover study comparing the efficacy of Creon® 25 000 and Panzytrat® within 28 days treatment periods in patients with pancreatic exocrine insufficiency caused by cystic fibrosis.

AIMS

The major aim of this study was to evaluate the efficacy and tolerance of Creon® 25 000 versus Panzytrat® in patients with pancreatic exocrine insufficiency caused by cystic fibrosis.

METHODS

Stool fat and stool weight were measured (g/24 hours) in stools collected during the last 72 hours of each treatment. The stool fat was analyzed centrally at center 1 (Dr. Henker, Dresden).

Other laboratory parameters were measured in the local center laboratories. Furthermore the daily intake of the drugs and stool frequency, frequency of abdominal pain and severity, nausea/vomiting, feeling of fullness, meteorism/flatulence were assessed on a daily basis by the patient on a diary card.
DRUGS AND DOSAGES

Creon® 25 000 is a pancreatin preparation of enteric-coated microspheres and one capsule contains 300 mg pancreatin with 25 000 units lipase, 18 000 units amylase and 1 000 units proteases according to the Pharmacopoeia Europea = Ph.Eur. (= FIP). In accordance with the United States Pharmacopoeia = USP: 25 000 units lipase, 74 700 units amylase and 62 500 units total proteases (conversion factor see Martindale 29).

Panzytrat® consists of enteric-coated tablets and one capsule contains 20 000 units lipase, 18 000 units amylase and 1 000 units proteases according to Ph.Eur. According to the USP one capsule contains: 20 000 units lipase, 74 700 units amylase and 62 500 units total proteases.

The dosage of each patient was individually based on the former treatment and expected intake of meals but should be constant during both study periods which lasted for 28 days each.

To maintain blindness identically appearing capsules were used.

PATIENTS ENTERED

A total of 90 cases were enrolled in the study in 4 centers. This number equals 89 patients, because one patient entered the study twice with an interval of about half a year with code numbers 1006 and 1022. The latter code number (1022) was excluded from all summary analyses.

In addition, one patient (code no. 3018) withdrew after randomization before intake of any study medication. Thus, a total number of 88 patients was included in the intent-to-treat and in the safety analysis.

PATIENTS PER CENTER

Center 1: 22
Center 2: 28
Center 3: 22
Center 4: 16

PATIENT CHARACTERISTICS

All patients analyzed proved to have pancreatic exocrine insufficiency caused by cystic fibrosis. 42 patients were males, 46 females. The age ranged from 3 - 29 years (mean 11.7 ± 6.0 years).
RESULTS

Dosage

Remarkable differences were recorded between the centers. The extent of the variation between centers is higher than between the study medications. During the last 4 days of each treatment period in mean the following dosages were administered:

<table>
<thead>
<tr>
<th>Center</th>
<th>Creon® 25 000</th>
<th>Panzytrat®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± SD</td>
<td>mean ± SD</td>
</tr>
<tr>
<td></td>
<td>[capsules/day]</td>
<td>[capsules/day]</td>
</tr>
<tr>
<td>1. Henker</td>
<td>6.7 ± 3.3</td>
<td>6.7 ± 3.2</td>
</tr>
<tr>
<td>2. Brömme</td>
<td>5.5 ± 2.2</td>
<td>5.6 ± 2.2</td>
</tr>
<tr>
<td>3. Klaer</td>
<td>4.0 ± 0.6</td>
<td>4.0 ± 0.6</td>
</tr>
<tr>
<td>4. Stern</td>
<td>10.2 ± 8.3</td>
<td>11.5 ± 10.5</td>
</tr>
<tr>
<td>Total</td>
<td>6.3 ± 4.5</td>
<td>6.5 ± 5.5</td>
</tr>
</tbody>
</table>

Stool fat

The extent in variation of stool fat is higher than originally assumed in the protocol. The analysis of variance showed no interaction between center and treatment sequence but borderline sequence influence. Nevertheless, the results of both periods were used to assess treatment and center effects. Stool fat was calculated to:

<table>
<thead>
<tr>
<th>Center</th>
<th>Creon® 25 000</th>
<th>Panzytrat®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric mean [g/day]</td>
<td>Geometric mean [g/day]</td>
</tr>
<tr>
<td>1. Henker</td>
<td>15.7</td>
<td>16.7</td>
</tr>
<tr>
<td>2. Brömme</td>
<td>13.6</td>
<td>14.6</td>
</tr>
<tr>
<td>3. Klaer</td>
<td>7.7</td>
<td>6.5</td>
</tr>
<tr>
<td>4. Stern</td>
<td>10.1</td>
<td>11.9</td>
</tr>
<tr>
<td>Total</td>
<td>11.6</td>
<td>11.9</td>
</tr>
</tbody>
</table>

Differences between centers have to be reported, but no treatment differences were detected.
Stool weight

No differences between the treatments were seen whereas remarkable differences occurred when comparing the results between the centers. It has to be referred to the highest value in center 3 and the lowest value in center 4.

Patients’ preference

In total, 28 patients (31.8%) preferred Creon® 25 000, 35 (39.8%) preferred Panzytrat® and 25 (28.4%) judged both treatments to be equal. Essential differences between the centers were found.

DIARY CARD PARAMETERS

All diary card parameters were analyzed for differences between the treatments. The variables were almost equally distributed in both treatment groups.

SAFETY DATA

For a total number of 63 out of 88 patients (71.6%) adverse events were reported. In 48 patients (54.5%) adverse events were observed under Creon® 25 000 treatment and in 42 patients (47.7%) under Panzytrat® treatment. The adverse events diarrhoea occurred more often (N = 8) under Panzytrat® than under Creon® 25 000 (N = 1).

The most adverse events affected the body as a whole with fever and infection. The digestive system was affected next frequently with anorexia and diarrhoea. Anemia is the most often recorded adverse event of the metabolic and nutritional disorders. The respiratory system was affected of 20.5% of the patients.

Two patients (code no. 1021 under Creon® 25 000, 2002 under Panzytrat®) suffered from subacute pulmonary exacerbation. Both were judged as being serious by the investigator due to hospitalization. Both events were rated as moderate and not related to study drug.

All adverse events for which severity ratings are available were rated as mild or moderate and no adverse event was judged probably or highly probably related to study drug.
CONCLUSION

- The large center effects and the high standard deviations led to limitations in the interpretation of the results but the two enzyme supplements seem to show similar efficacy.

- No differences between the treatments were obtained concerning efficacy parameters.

- A substantial number of patients had abnormal stool fat values during treatment and are therefore considered to have been underdosed.

- The safety profile is good for both drugs although more often diarrhoea was reported in the Panzytrat® group.