1. SUMMARY

TITLE

Randomized, open-label, cross-over study comparing the efficacy and tolerance of Creon® Forte (Creon® 25000) and Cotazym S Forte® in children and young adults with cystic fibrosis

INVESTIGATOR

Removed for privacy reasons

STUDY DESIGN

This was an open-label, randomized, two-period, cross-over study in children and young adults with cystic fibrosis who were currently receiving pancreatic enzyme supplementation with Cotazym S Forte®. The study consisted of two 2-week treatment periods preceded by a dose optimization period of 2-4 weeks.

AIMS

Primary aim of this study was to compare the coefficient of fat absorption during treatments with Creon® Forte (Creon® 25000) and Cotazym S Forte® at doses providing at least equivalent lipase activity, based on a pre-study dosage of Cotazym S Forte®. Furthermore patient's symptoms of disease (abdominal pain, abdominal bloating, diarrhea, constipation, nausea, vomiting and anorexia) were to be assessed as well as the safety and tolerance of Creon® Forte capsules. Faecal nitrogen was planned to be assessed as well but was not measured.

METHODS

The coefficient of fat absorption was calculated from the fat content of the stools collected during the last 3 days of each treatment period and the average fat intake on the day before, and the days of the stool collection. The patients' drug preference had to be asked for at the end of the study. The number of stools per day and the intensity of abdominal pain, constipation, nausea, vomiting and anorexia had to be assessed daily by the patients/guardians. Furthermore, the efficacy was assessed by the investigator at the end of each treatment period based on these parameters.
DRUGS AND DOSAGES

Creon® Forte (Creon® 25000) is a pancreatin preparation with each capsule containing 25000 BP units of lipase, 18000 BP units of amylase and 1000 BP units of protease. BP units of pancreatic extract = Ph.-Eur. units.

One capsule of Cotazym S Forte® contains 10000 BP units of lipase, 4200 BP units of amylase and 410 BP units of protease.

The number of Creon® Forte capsules to be taken was calculated from a conversion table (see Appendix II of the study protocol) based on the number of Cotazym S Forte® capsules taken after dose optimization.

PATIENTS ENTERED

A total of 18 patients entered this study, 7 of whom were randomly allocated to the treatment sequence Creon® Forte followed by Cotazym S Forte® and 7 to the treatment sequence Cotazym S Forte® followed by Creon® Forte, 4 patients entered the screening period of the study but were withdrawn before randomization. All 14 patients randomized to treatment completed both treatment periods.

The trial was stopped prematurely by the investigator and the Ethics Committee due to the discussion that the therapy with high-strength pancreatic enzyme supplementation would be involved in the occurrence of fibrosing colonopathy in young cystic fibrosis patients. However, it was subsequently proven by an epidemiological study (Smyth et al. 1995, 11) in the UK that Creon® 25000 is not associated in the occurrence of fibrosing colonopathy in cystic fibrosis patients.

PATIENT CHARACTERISTICS

Mean age of the randomized patients was 9 years (range 3 - 16 years) with the mean duration of cystic fibrosis being 8 years. Nine patients were male and 5 patients were female. All patients were Caucasians.

RESULTS

Efficacy

The coefficient of fat absorption was very similar in both treatment groups with an adjusted mean of 89% under Creon® Forte and of 91% under Cotazym S Forte®. The 95% confidence interval for the coefficient of fat absorption ranged from -4.7% to 1.0% indicating equivalent effectiveness of the two treatments, as the interval lies completely within the equivalence range of ± 5%.

All 14 patients who were analyzed for efficacy preferred treatment with Creon® Forte.
The overall assessment of efficacy by the investigator with respect to abdominal pain, abdominal bloating, diarrhea, constipation, nausea and vomiting and anorexia was very similar for both treatments. For most of the symptoms asked for, the assessment was good or very good for the majority of patients under both treatments. The only symptoms with ratings other than good or very good were abdominal pain where the assessment was moderate for 3 patients (Pat No. 3, 8 and 11) under both treatments and nausea and vomiting where an assessment of moderate was made for one patient under treatment with Creon® Forte.

Diary card parameters

Eleven patients had abdominal pain on at least one day during treatment with Creon® Forte and 8 patients on at least one day during treatment with Cotazym S Forte®. The percentage of days of presence was, in the median, higher during treatment with Creon® Forte (15%) as compared to treatment with Cotazym S Forte® (7%). Constipation was reported by one patient on 2 days during treatment with Cotazym S Forte® with an average intensity of 1 (mild). Nausea was present at least once for 4 patients during treatment with Creon® Forte and for 3 patients during treatment with Cotazym S Forte®. Two patients suffered from vomiting during treatment with Creon® Forte and one patient during treatment with Cotazym S Forte®. Anorexia was documented in one patient on one day during Creon® Forte treatment (mild intensity) and in one patient on one day during treatment with Cotazym S Forte® (mild intensity).

Safety data

Two serious adverse events occurred during the run-in period under Cotazym S Forte® therapy: Pat.no. 2 had an acute bowel obstruction that was treated successfully by an enema and pat.no. 3 showed a chest infection.

Eleven patients reported at least one adverse event during treatment with Creon® Forte and 10 patients reported at least one adverse event during treatment with Cotazym S Forte®. Adverse events considered to be treatment emergent were documented for 10 patients during treatment with Creon® Forte and for 8 patients during treatment with Cotazym S Forte®. For all adverse events the relationship to the study medication was considered to be doubtful in the opinion of the investigator. The adverse event most frequently reported was increased cough reported for 6 patients during treatment with Creon® Forte and 3 patients during treatment with Cotazym S Forte®, respectively.

There were only minor changes in body weight for all patients when comparing weight before and after the respective treatment period. On the average, no major differences occurred under both Creon® Forte and Cotazym S Forte® with respect to blood pressure and heart rate.

The overall assessment of tolerability by the investigator and the patients was good or very good in all cases.
CONCLUSION

• Pancreatic enzyme replacement with Creon® Forte led to a similar coefficient of fat absorption as compared to Cotazym S Forte® (adjusted mean of 89% for Creon® Forte, 91% for Cotazym S Forte®) even with the low number of 14 patients. A clinically irrelevant difference of ± 5% was reached.

This effect could be achieved with only 43 % of the number of Creon® Forte capsules compared to Cotazym S Forte®.

• All 14 patients preferred treatment with Creon® Forte.

• Both drugs were well tolerated.