1. SUMMARY

TITLE

Double-blind, randomized, cross-over study comparing the efficacy and tolerance of Creon® and Pancrease® in children and young adults with cystic fibrosis

INVESTIGATOR

Removed for privacy reasons

STUDY DESIGN

This was a double-blind, randomized, cross-over study comparing the efficacy and tolerability of Creon® and Pancrease® in children and young adults suffering from pancreatic exocrine insufficiency due to cystic fibrosis.

Double blindness of the study was confirmed by the investigator (see investigator's statement concerning blindness, appendix A-3).

In Phase I patients were receiving Creon® and were titrated to an individually optimal dose.

They then entered the cross-over Phase II in which they were treated with Creon® for 28 days followed by Pancrease® for 28 days or vice versa. Dosage in Phase II was based on an equivalent lipase content of Creon® and Pancrease® as titrated in Phase I, but a different number of capsules had to be taken.

AIMS

The primary aims of the study were to compare Creon® and Pancrease® regarding the coefficient of fat absorption and the coefficient of nitrogen absorption. Secondary aims were to compare the two treatments with respect to stool frequency, stool weight, and to assess their tolerability.
METHODS

Fat and nitrogen absorption, stool frequency and stool weight were determined from stool collected by the patients over a duration of 72 hours, and from a careful qualitative and quantitative characterization of food intake. Further evaluations were based on patient diary cards, patient's preference of treatments, body weight, and the reported adverse events.

DRUGS AND DOSAGES

Creon® capsules containing declared 8 000 FIP units (= Ph.Eur. units) of lipase, 9 000 FIP units of amylase and 450 FIP units of total proteases, and Pancrease® capsules containing declared 5 000 BP units of lipase, 3 000 BP units of amylase and 350 BP units of free proteases were used. In accordance with the United States Pharmacopoeia = USP one capsule Creon® contains declared 8 000 units lipase, 37 350 units amylase and 28 125 units total proteases; and one capsule Pancrease® contains declared 5 000 units lipase, 12 450 units amylase and 21 875 units free proteases (conversion factor see Martindale 29). All patients received Creon® capsules and Pancrease® capsules at an individually titrated fixed dose based on identical declared lipase activity in a randomized order.

PATIENTS ENTERED

A total of 29 patients entered the study. Two patients withdrew after Visit 1, while the other 27 patients entered and completed both treatment periods in Phase II.

PATIENT CHARACTERISTICS

Of the 27 patients completing the study, 12 were male and 15 were female. Mean age was 10.3 years (range 5.9 - 18.3 years), mean weight was 31.9 kg (range 20.9 - 55.8 kg), and mean duration of cystic fibrosis was 9 years (range 5.9 - 15.6 years).

RESULTS OF EFFICACY ANALYSES

Mean values of fat absorption were 90% for both treatments and the 95% confidence interval indicated that the treatments differ by at most 2.6%. Mean values of nitrogen absorption were slightly smaller but also nearly identical for both treatments (86%) and again the treatment difference is bounded by 2.5%. Between the two treatment sequences no major differences were apparent. Therefore the two treatments are considered as equivalent regarding the primary efficacy parameters CFA and CNA.

Stool fat and stool weight were also similar between the two treatments, however, the statistical uncertainty was larger.
DIARY CARD PARAMETERS

No differences were detected between the two treatments regarding diary card parameters.

PATIENTS PREFERENCE

The majority of patients preferred Creon® (19 patients, 70%). Three patients (11%) preferred Pancrease® and 5 patients (19%) expressed no preference.

RESULTS OF SAFETY ANALYSES

Treatment emergent adverse events were reported for 11 patients (41%) during Phase I, for 13 patients (48%) during Creon® treatment, and for 12 patients (44%) during Pancrease® treatment. In Phase II on both treatments most frequently events occurred in the body as a whole, the digestive system, and the respiratory system, and the most frequent adverse events were abdominal pain and nausea. No major treatment differences were apparent.

Seriousness was not defined in the CRF, and is therefore not summarized.

Patient 3 was admitted to hospital after treatment period B (Creon®). The reason for the hospitalization were respiratory problems (a central cyanosis of mild intensity, a deteriorated exercise tolerance of moderate intensity, increased sputum and worsening cough both of severe intensity) which had a slow onset one month before the last visit. No statement about the cessation of the symptoms was made.

No patient died during the study, and no patient was withdrawn due to adverse events.

CONCLUSION

Similarly good therapeutic effects can be achieved with equal lipase units of Creon® and Pancrease® concerning fat and protein digestion in CF-patients suffering from maldigestion due to pancreatic exocrine insufficiency.

The number of capsules to be taken daily by the patients is considerably smaller (approximately half) in case of Creon®. This is supposed to be the major reason for the significant treatment difference in patient's preference in favour of Creon®.

Both drugs were equally well tolerated.