1. SUMMARY

TITLE

$^{13}$CO$_2$ breath test with $^{13}$C-labelled hiolein for the non-invasive determination of exocrine pancreatic function in healthy subjects and in patients with cystic fibrosis:

Efficacy assessment of pancreatic enzyme replacement in children with cystic fibrosis.

INVESTIGATOR

STUDY DESIGN

Study plan

The study was planned as an open study with a six-day placebo run-in period followed by a six-day treatment period under Kreon® in CF-patients. Healthy children served as controls.

Study performance

The study was performed as a double-blind, not-randomized, single-center, two-period sequence study with the administration of Kreon® or placebo. In the first period the CF-patients received Kreon® and in the second period placebo. Each period lasted 6 days. Healthy children served as controls included only in one period and not receiving any treatment.

AIMS

The aims of this study were

- to evaluate the efficacy of pancreatic enzyme replacement therapy in children with cystic fibrosis.

and

- to validate the $^{13}$CO$_2$-hiolein breath test as a diagnostic technique for the quantitative assessment of exocrine pancreatic insufficiency.

The results of the $^{13}$CO$_2$-hiolein breath test were to be compared with those of established other non-invasive techniques for diagnosing pancreatic function in children.
METHODS

On Day 4 of both periods a rice breath test was performed after a standardized meal of rice. On Day 5 of both periods the combined rice-hiolein breath test was performed in which $^{13}$C-labelled hiolein was added to the standard rice meal. During both breath tests $\text{H}_2$-values and delta-values were determined. The delta-value was calculated as the difference in the $^{13}\text{CO}_2$ concentration between the taken breath sample and to the known concentration of a standard gas ($\%$). In both periods 3 day-stool collection was performed from Day 4 to Day 6, of which stool fat, chymotrypsin, and stool weight were analyzed.

DRUGS AND DOSAGES

Only patients received treatment with Kreon®. The number of capsules to be taken per day was to be adjusted to 1 500 lipase units per kg body weight, respectively 1 000 lipase units per g fat intake, according to Ph. Eur. and according to USP. Duration of treatment was 6 days.

PATIENTS ENTERED

Twelve healthy children and 11 children with cystic fibrosis entered the study and all of them completed the study. Only the 11 patients received treatment with Kreon® and placebo.

PATIENT CHARACTERISTICS

Of the healthy children, 6 were male and 6 female. The mean age was $11.5 \pm 2.4$ years. Of the children with cystic fibrosis, 4 were male and 7 female. The mean age was $10.2 \pm 3.0$ years. One patient was of oriental origin, all other were caucasian. Pancreatic exocrine insufficiency was proven in 8 patients by sweat analysis and in 3 patients by stool analysis.

RESULTS OF EFFICACY ANALYSES

Statistically significant differences were found between healthy children and placebo treated CF children. Nearly no differences were detected between Kreon® treated CF patients and healthy volunteers. A statistically significant difference was demonstrated between placebo-treated and Kreon® treated CF patients.

Stool analysis showed statistically significant differences between healthy children and placebo-treated children with CF regarding stool fat, chymotrypsin and stool weight. The comparison between Kreon® and placebo treatment revealed clear differences in favour of Kreon, although with this low number of patients ($N = 7$) statistically significant results were only obtained for stool weight.

The combined $^{13}\text{CO}_2$ breath test was validated as a sensitive method for the diagnostic verification of pancreatic exocrine insufficiency.

RESULTS OF SAFETY ANALYSES

The safety of Kreon® was good in cystic fibrosis patients. No adverse event was reported during this study; "hunger" was reported by 4 patients as a complaint during test procedures.
CONCLUSION

- Kreon® has proven to be statistically significantly effective in the therapy of pancreatic exocrine insufficiency caused by cystic fibrosis:

  Results of the combined $^{13}$CO$_2$-hiolein breath test in patients under Kreon® therapy are comparable to those of healthy volunteers; a statistically significant difference was found between Kreon® and placebo therapy in cystic fibrosis patients. The Kreon® treated patients showed a comparable digestion as healthy children. The results of stool analysis supported these data.

- Due to the study design it was not possible to differentiate between treatment and time effects.

- The combined $^{13}$CO$_2$-hiolein breath test is valid as a sensitive diagnostic method for the diagnosis of pancreatic exocrine insufficiency.

- The safety of Kreon® was good in cystic fibrosis children and confirmed the experiences of other clinical trials.