1.0 SYNOPSIS

This trial was an open label, multi-center, randomized, two-period crossover study to compare the tolerance, gastrointestinal effects, and patient preference for Creon 25, a new higher dose pancreatic enzyme supplement, with Creon, a currently available enzyme supplement. The study enrolled a total of thirty-three (33) cystic fibrosis patients, 6 to 22 years of age, at two investigative sites.

The specific objectives of the study were to:

- compare patient tolerance to test (Creon 25) and reference (Creon) pancreatic enzyme supplements as measured by the occurrence of episodes of abdominal pain, bloating, nausea and vomiting, constipation or diarrhea, gas, and the number of bowel movements per day;

- compare fecal fat excretion and the coefficient of fat absorption (CFA) during the treatment phases of Creon 25 and Creon.

- to compare patient preference for test vs reference Creon in cases of pancreatic exocrine insufficiency.
Patients with cystic fibrosis, who were currently receiving at least 72,000 units of lipase per day of a commercially available enzyme preparation for their pancreatic exocrine insufficiency, were assigned to a 7 to 10 day stabilization period (Phase I) on the currently available supplement, Creon, at a dosage at least equivalent to their pre-study lipase dosage. If necessary, titrations of dose were allowed for symptom control.

After the patients stabilized on the Phase I Creon regimen, they entered Phase II (a 14-day therapy period) and were randomly assigned to receive either Creon at the same dose as the stabilization period, or to an equivalent Creon 25 in a dose of two-thirds fewer capsules than the Creon dose. Creon 25 has the advantage of providing higher enzyme content and therefore requires fewer capsules. On the afternoon of Day 11 of Phase II, the patient entered the hospital for a strictly controlled diet during a three-day stay. A 72 hour collection of stool was examined for coefficient of fat absorption, stool weight, nitrogen content and other factors. Following the 3-day hospital stay at the end of Phase II, the patient entered into Phase III by being crossed over to the other medication (Creon 25 or Creon). On the afternoon of day 11 of Phase III, the patient again entered the hospital for an identical three day stay as in Phase II.

Thirty-five (35) patients at two sites were screened for this open label comparison of Creon vs the new Creon 25 formulation. Thirty-three (33) patients were found to be eligible and were entered into the study, and 30 patients completed all 3 phases of the study. One patient discontinued the trial during the first of 3 study phases, and 2 patients discontinued before the start of the third study phase.

There were six serious adverse events reported during this study. There was one death, and there were five hospitalizations. The death was reported by the
physician as not related to the drug. These adverse experiences are commonly seen in this patient population. None are considered to be related to drug treatment by Creon or Creon 25.

Non-serious adverse experiences noted by the patients were generally related to the underlying conditions found in these patients with cystic fibrosis. The most common adverse events were headache (n = 6 patients = 18.2%), fever, abdominal pain and pneumonia (n = 5 each = 15.2%), back pain (n = 4 = 12.1%), and rhinitis, pain, infection, and rash (n = 3 each = 9.1%).

The few adverse experiences that were reported "possibly" related to Creon 25, including 3 instances of abdominal pain, 2 instances of dyspepsia, and single instances of abnormal stool, GI hemorrhage, and constipation in 6 of the 33 patients (18.2%), were probably related to the underlying disease conditions, and possibly to a greater intake of fat during Creon 25 treatment (more of the available food was eaten during the Creon 25 treatment). None of the adverse experiences reported during Creon administration periods was considered "possibly" related to drug. All such experiences were seen as "unrelated" or of "unlikely" relationship to drug.

Both Creon and Creon 25 were equally safe in patients with cystic fibrosis and pancreatic insufficiency.

The two treatments were statistically equivalent with respect to the coefficient of fat absorption (CFA), dietary fat intake and average stools per day and were statistically similar in stool marker transit time, fecal fat excretion and stool nitrogen content. The statistical power to detect treatment differences in CFA
exceeded 99%. Each treatment appears to be equally effective when used as an adjunct in cystic fibrosis patients with chronic pancreatic insufficiency.

Creon 25 was preferred over the regular Creon by 66.7% of patients over the regular Creon (20 of 30 patients indicated they preferred Creon 25; 5 of 30 patients preferred Creon; 5 patients indicated no preference or had no response). This result was probably due to the fact that, as according to the protocol, two-thirds fewer Creon 25 capsules were taken with each meal.

During the 72-hour hospital stay for monitoring of dietary fat intake and fecal fat excretion, patients taking Creon 25 exhibited a higher (21 gm/72hr, or about 9% greater, p = .0239) average dietary fat intake than when they took regular Creon. There was also about 12% more fat excreted in the feces when the patients were taking Creon 25 than when they took regular Creon.

The greater dietary fat intake, and greater fecal fat excretion, during Creon 25 administration can be explained by the fact that more of the special diets were eaten during Creon 25 administration.

After each special meal during the 72-hour hospitalization period, the amount of fat eaten was recorded. These data indicated that patients ate more fat during Creon 25 treatment than during Creon treatment, but the reason for this finding is not clear. Because diets were the same for each dosing phase, and the dosing was randomized, the higher intake of fat can only be explained if patients ate more of the food available during Creon 25 than Creon treatment.

In spite of the greater fat intake and excretion, the new, higher dose Creon 25 was equally as effective as the standard Creon in treating the pancreatic
insufficiency of patients with cystic fibrosis. Creon 25 was also preferred as a dosage form over Creon by these patients.