SYNOPSIS

TITLE: A Comparison of the Efficacy and Safety of CREON®20 and Placebo in the Treatment of Steatorrhea in Adult Cystic Fibrosis Patients with Clinical Exocrine Pancreatic Insufficiency

INVESTIGATORS: Removed for privacy reasons

OBJECTIVES: The primary objective of this study was to compare the effectiveness of CREON®20 (pancrelipase) Delayed-Release MINIMICROSPHERES® Capsules to placebo in the treatment of steatorrhea in cystic fibrosis patients (≥ 18 years) with exocrine pancreatic insufficiency who were maintained on a high fat (approximately 100 g/day) diet. The change from open-label (baseline) to double-blind (final) assessment in the coefficient of fat absorption (CFA) was the primary efficacy measure.

The secondary objectives of this study were to compare the effects of treatment on frequency of bowel movement, stool consistency, clinical global improvement (CGI) and safety following administration of CREON®20 Capsules or placebo.

STUDY DESIGN: This was a randomized, double-blind, parallel group, multicenter study with an open-label CREON®20 run-in phase. Patients with a CFA greater than 80%, as determined by a 72-hour stool collection performed after stabilization on open-label CREON®20 treatment, were randomized to receive CREON®20 Capsules or placebo treatment during the double-blind phase. After a minimum of two days of double-blind treatment, a repeat 72-hour stool collection was performed.

PATIENT POPULATION: Cystic fibrosis patients with clinical exocrine pancreatic insufficiency who were ≥ 18 years of age were invited to participate in the study. A minimum of 40 evaluable patients were planned to complete the double-blind treatment phase.

TREATMENT SUMMARY: Open-label CREON®20 dose was individualized for each patient while on a high fat diet using clinical symptoms as a guide. Once stabilized on dose (minimum of 2 days) and diet (minimum of 3 days), a 72-hour inpatient stool collection was performed. The open-label treatment phase continued until fecal fat results were received. Open-label treatment was 2-3 weeks for most patients.
Patients qualifying for entry into the double-blind phase were randomized to placebo or CREON®20 Capsules at the same number of capsules taken at the end of the open-label CREON®20 treatment phase. After a minimum of 2 days of double-blind treatment, a 72-hour stool collection was performed. Double-blind treatment ranged from 5-8 days depending on gastrointestinal transit time determined by orally ingested stool markers.

**STUDY STATUS:** Completed.

**RESULTS: PATIENT INFORMATION:** Fifty cystic fibrosis patients were entered into the open-label phase at six investigative centers. These patients were representative of the general adult cystic fibrosis population, as evidenced by medical history taken at screening. Of the 50 patients, 36 (18 placebo, 18 CREON®20) were randomized to double-blind treatment and 34 (17 placebo, 17 CREON®20) of those 36 patients successfully completed the study. The 36 patients randomized to double-blind treatment made up the intent-to-treat (ITT) population. All patients in the ITT population were Caucasian consisting of 22 males and 14 females ranging in age from 18 to 53.5 years (mean age 23.8 years). There were no significant differences between groups for age, sex or race. Protocol deviations were considered minor and did not result in the exclusion of data from the analyses.

**RESULTS: EFFICACY:** A statistically significant treatment improvement following CREON®20 treatment was achieved for the primary efficacy parameter, change from open-label to double-blind CFA (p<0.001), and all secondary efficacy parameters; change from open-label to double-blind stool frequency (p<0.001), stool consistency (p=0.001), and CGI (p<0.001) compared to placebo.

**RESULTS: SAFETY:** A treatment difference was seen in the number of placebo patients reporting abdominal pain, flatulence, nausea, and diarrhea in the double-blind treatment phase compared to those taking CREON®20 Capsules. This was supported by end of study physical exam findings where more placebo than CREON®20 patients had abdominal tenderness or distension. There were no treatment differences between CREON®20 and placebo in change from open-label to double-blind serum and urinary uric acid concentrations, and number and frequency of markedly abnormal vital signs and laboratory values.

**CONCLUSIONS:** CREON®20 Capsules are effective in the treatment of steatorrhea associated with exocrine pancreatic insufficiency in adult patients diagnosed with cystic fibrosis. The use of CREON®20 Capsules in adults with cystic fibrosis is safe at the doses used (mean dose ranging from approximately 1000-12,300 lipase units/kg/day) to control the symptoms of fat malabsorption in this clinical trial.