

A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Cross-Over Study to Evaluate the Effectiveness and Safety of a Novel Pancrelipase (PANCRECARB® MS-16) in Reducing Steatorrhea In Children and Adults with Cystic Fibrosis

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ABSTRACT

Background: Pancreatic enzyme replacement therapy (PERT) is used to treat the malabsorption associated with exocrine pancreatic insufficiency (EPI) in cystic fibrosis (CF). This trial evaluated the efficacy and safety of a novel pancrelipase (PANCRECARB® MS-16) in children and adults with CF.

Methods: CF subjects with EPI (confirmed by fecal elastase) currently receiving PERT with a commercially available pancreatic enzyme were enrolled into a randomized, double-blind, placebo-controlled, multi-center, crossover study. During a dose stabilization period, subjects began open-label PANCRECARB® MS-16, consumed a high-fat diet (≥ 2 gm/kg body weight/day), and subjectively optimized their dose of PANCRECARB® MS-16. This was followed by a treatment period where subjects were randomized to receive active study drug (PANCRECARB® MS-16) or placebo for 5 days. The high-fat diet was continued. A 72-hour stool collection using dye markers (begun on day 3 as an in patient) was obtained for fat and protein determination. A washout/re-stabilization period of 7-10 days followed with subjects on open-label PANCRECARB® MS-16. Subjects were then crossed over to either active study drug or placebo, remained on the high-fat diet, and a second 72-hour stool collection using dye markers was performed. The change in percent coefficient of fat absorption (%CFA) and nitrogen absorption (%CNA) was calculated from the 72 hour stool collection and dietary records. The %CFA and %CNA observed during treatment with active study drug (PANCRECARB® MS-16) was compared to that of placebo. %CFA was defined as [(total fat intake (g) - total fat excretion (g))/total fat intake(g)]x 100. CNA was determined similarly.

Results: Twenty-nine subjects were enrolled, 24 randomized, and 21 (10 children \geq age 7 years, 11 adults \geq age 18 years) completed the study. The %CFA with PANCRECARB® MS-16 treatment was 82.5 compared to 46.3 with placebo (difference 36.2, $p < 0.001$); a 78.1% improvement in fat absorption with PANCRECARB® MS-16 compared to placebo. The %CNA with PANCRECARB® MS-16 treatment was 79.0 compared to 47.2 with placebo (difference 31.8, $p < 0.001$); a 67.4% improvement in nitrogen absorption with PANCRECARB® MS-16 compared to placebo. The overall stool frequency with PANCRECARB® MS-16 treatment was 6.1 bowel movements/72 hrs compared to 10.1 with placebo ($p < 0.001$); 39.6% fewer bowel movements with PANCRECARB® MS-16. Stool weight was 49.9% less with PANCRECARB® MS-16 compared to placebo ($p < 0.001$). Responses to treatment with PANCRECARB® MS-16 were similar in children and adults for all efficacy endpoints. The most commonly reported treatment emergent adverse events (AEs) for both PANCRECARB® MS-16 and placebo were abdominal pain and upper abdominal pain, with fewer subjects reporting gastrointestinal AEs during PANCRECARB® MS-16 treatment than during placebo.

Conclusion: The results of this study confirm the efficacy and safety of a novel pancrelipase (PANCRECARB® MS-16) in CF children and adults with EPI.

INTRODUCTION

Background

- Exocrine pancreatic insufficiency (EPI) occurs in approximately 90% of patients with cystic fibrosis (CF).
- Fat and protein maldigestion results in malnutrition and growth failure.
- Effective correction of maldigestion is critical to the survival and well-being of patients with CF.
- Pancreatic enzyme replacement therapy (PERT) has been standard of care for more than 50 years for the treatment of EPI in patients with CF.
- PANCRECARB® MS-16 (pancrelipase) capsules containing enteric-coated, bicarbonate-buffered microspheres have been used by patients with CF for the treatment of EPI for more than a decade.

Objectives

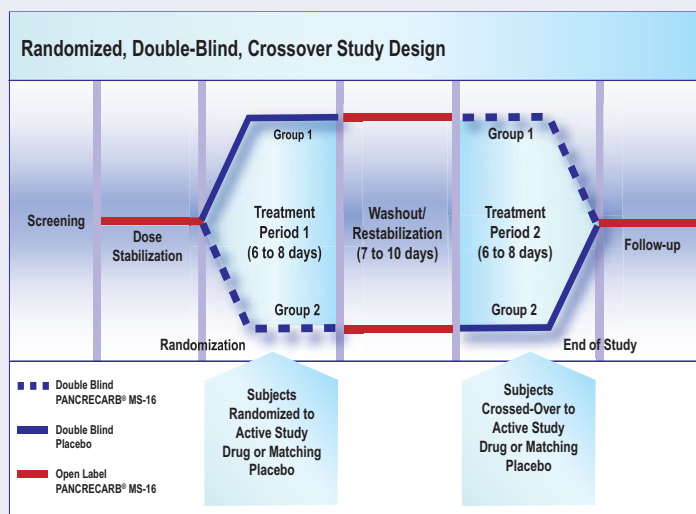
- Primary Objective: Determine the efficacy and safety of PANCRECARB® MS-16 (pancrelipase) in reducing steatorrhea (as measured by 72-hour stool fat determinations) in children and adults with CF and EPI.

- Secondary Objectives: Determine the efficacy and safety of PANCRECARB® MS-16 (pancrelipase) in reducing fecal nitrogen loss (as measured by 72-hour stool nitrogen determinations) in children and adults with CF and EPI. Evaluate stool frequency and stool weight.

Inclusion/Exclusion Criteria

- Age ≥ 7 years.
- Confirmed diagnosis of cystic fibrosis (CF).
- EPI demonstrated by fecal elastase ≤100 µg/g stool.
- Adequate nutritional status based on body mass index (BMI).
 - Age 7-20 yrs old - BMI ≥ 5th percentile for age.
 - Age > 20 yrs old - BMI for females ≥ 16.0
 - BMI for males ≥ 16.5
- Receiving pancreatic enzyme replacement therapy with a commercially available pancreatic enzyme product.
- Subjects were excluded if they had a medical condition that the investigator deemed significant enough to interfere with the ability of the subject to participate in the trial or interfering with assessment of effects of enzyme therapy on fat absorption.

METHODS



Study Design

- Randomized, double-blind, placebo-controlled, multi-center, crossover study.
- Standard diet high in fat content (≥2 gm/kg body weight/day) during each treatment period (72-hour controlled diet period) in a General Clinical Research Center (GCRC), and at home.
- 72-hour stool collection using dye markers was obtained for fat and protein determination during treatment period in a GCRC.

- Dosing as determined during the Dose Stabilization Period.
- Washout/Re-Stabilization Period, subjects were treated with open-label PANCRECARB® MS-16 (determined during the Dose Stabilization Period).
- Subjects crossed over to either active study drug or matching placebo.
- %CFA and %CNA observed during treatment with active study drug (PANCRECARB® MS-16) was compared to that of placebo.

Efficacy and Safety Endpoints

- Primary Endpoint:
 - Change in percent coefficient of fat absorption (%CFA)
 - $$\% \text{ CFA} = \frac{\text{total fat intake (g)} - \text{total fat excretion (g)}}{\text{total fat intake (g)}} \times 100$$
- Secondary Endpoints:
 - Change in percent coefficient of nitrogen absorption (% CNA)
 - Change in stool frequency
 - Change in stool weight
- Safety Endpoints:
 - Clinical laboratory parameters
 - Physical examination findings and vital signs
 - Severity, frequency, and duration of adverse events (AEs)

RESULTS

Baseline Demographics

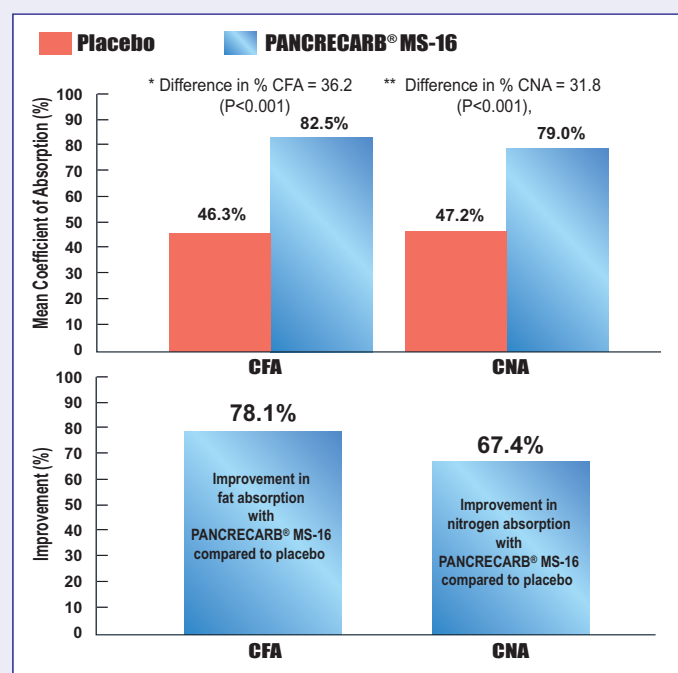
	Children (n = 11)	Adults (n = 13)	Overall (n = 24)
Age (years)			
Mean (SD)	11.8 (2.96)	26.5 (7.40)	19.8 (9.41)
Gender, n (%)			
Male	8 (72.7%)	10 (76.9%)	18 (75.0%)
Female	3 (27.3%)	3 (23.1%)	6 (25.0%)
Race, n (%)			
White	13 (0.0%)	11 (84.6%)	22 (91.7%)
Black	0 (0.0%)	2 (15.4%)	2 (8.3%)
Weight (kg)			
Mean (SD)	40.21 (11.765)	58.76 (7.596)	50.26 (13.3)

Medical history, past surgical procedures, and concomitant medications, therapies, and non-drug treatments were all consistent with those typically seen in patients with CF.

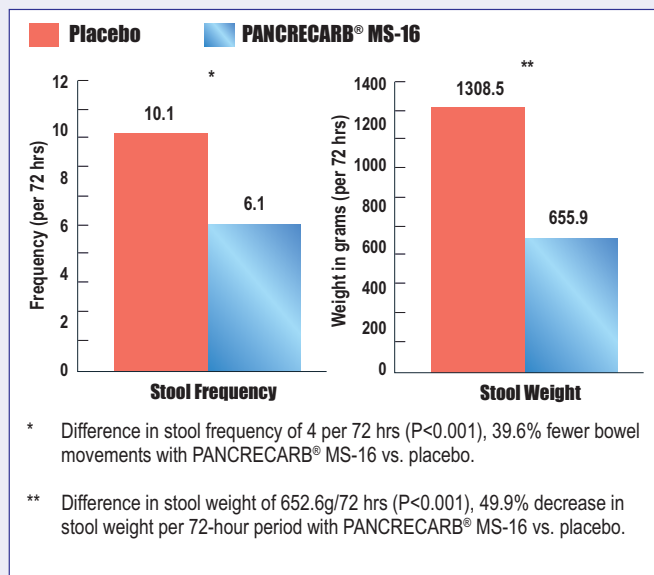
Subject Disposition

- 29 subjects were enrolled (14 children aged ≥ 7 to 17 years and 15 adults aged ≥ 18 years).
- 24 subjects were randomized (11 children, 13 adults).
- 21 subjects completed the study (10 children, 11 adults).

Efficacy



Efficacy (cont'd)



- Responses to treatment with PANCRECARB® MS-16 were similar in children and adults for all efficacy endpoints.

Safety

- 20 of 24 subjects randomized reported 105 treatment-emergent AEs. The most commonly reported AE for both PANCRECARB® MS-16 and placebo was abdominal pain (14.3% for PANCRECARB® MS-16 vs. 25.0% for placebo).
- All AEs were assessed as mild or moderate in severity.
- Total of 105 AEs (46.0% for PANCRECARB® MS-16 vs. 54.0% for placebo).
- No serious AEs or deaths were reported.
- Two subjects had AEs reported that led to study withdrawal (while on placebo).
- Treatment with PANCRECARB® MS-16 had no clinically significant effects on hematology, chemistry, or urinalysis parameters.
- No trends of clinical concern were observed in the change from baseline for any vital sign finding or body weight throughout the study.

CONCLUSIONS

- All efficacy measures were significantly ($p < 0.001$) improved when compared to placebo, demonstrating the contribution of PANCRECARB® MS-16 to the correction of steatorrhea (i.e., improvement in fat and nitrogen absorption, and reduction in overall stool frequency and weight).
- Analysis of safety measures revealed no clinically significant changes in laboratory parameters, with the most commonly reported treatment-emergent AEs being mild to moderate gastrointestinal symptoms which are expected in this patient population.
- The results of this study confirm the efficacy and safety of PANCRECARB® MS-16 in CF patients with EPI.

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