CLINICAL
INVESTIGATION

Efficacy and safety of a unique enteric-coated bicarbonate-buffered pancreatic enzyme replacement therapy in children and adults with cystic fibrosis

Background: Pancreatic enzyme replacement therapy (PERT) is used to treat exocrine pancreatic insufficiency in cystic fibrosis. **Results/Methods:** Efficacy and safety of a unique enteric-coated (EC) bicarbonate-buffered PERT product (PERTZYE®/PANCRECARB®; Digestive Care, Inc., Bethlehem, PA, USA) was studied in a randomized, double-blind, placebo-controlled cross-over design. Subjects were stabilized on EC-bicarbonate-buffered PERT and a high-fat diet. During two treatment periods, subjects were randomized to EC-bicarbonate-buffered PERT or placebo, followed by a 72-h stool collection employing an ingested stool dye marker. Mean coefficient of fat absorption with EC-bicarbonate-buffered PERT was 82.5% compared with 46.3% with the placebo (absolute difference 36.2%; p < 0.001), a 78.2% improvement for active over placebo. Similar improvements in nitrogen absorption were observed. Overall stool frequency and stool weight decreased (p < 0.001). No safety concerns were identified. **Summary:** EC-bicarbonate-buffered PERT is effective in treating cystic fibrosis-associated exocrine pancreatic insufficiency.

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The majority of people with cystic fibrosis (CF) have exocrine pancreatic insufficiency (EPI) and require pancreatic enzyme replacement therapy (PERT) [1,2]. Oral administration of porcine-derived pancreatic enzyme products containing pancrelipase with meals has long been and continues to be the standard of care for treating EPI associated with CF and other conditions affecting the exocrine pancreas [3]. Currently, most formulations encase pancreatic enzymes in a pH-sensitive enteric coating (EC) to prevent gastric acid inactivation in the stomach, allowing enzyme delivery to the lumen of the duodenum [4]. However, a less than optimal clinical response may occur in CF patients taking conventional EC-PERT due to a number of confounding factors, including suboptimal enzyme activation in the duodenum because of a low pH environment that occurs in this patient population [5].

A unique EC-bicarbonate-buffered PERT formulation (PERTZYE®/PANCRE-CARB®; Digestive Care, Inc., Bethlehem, PA, USA) was developed to optimize the pH in the microenvironment surrounding the microspheres. The buffering capacity is preserved by the EC until release of the enzymes in the upper intestine. EC-bicarbonate-buffered PERT has previously been shown to produce a significant increase in fat absorption in CF patients compared with treatment with EC-nonbuffered PERT at equivalent lipase doses [6]. The present study assessed the effectiveness and safety of EC-bicarbonate-buffered PERT compared with placebo in

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improving the absorption of fat and protein (measured as absorption of nitrogen) in children and adults with CF-associated EPI.

Methods

This multicenter, prospective, randomized, double-blind, placebo-controlled cross-over study evaluated the efficacy and safety of EC-bicarbonate-buffered PERT in treating CF-associated EPI. The study followed the guidelines recommended by the US FDA for designing clinical trials evaluating PERT products for marketing approval by the US FDA [7]. The study was performed at five centers in the USA and consisted of six periods: a 4-day screening period to determine eligibility; a 7–10-day dose-stabilization period; two 6–8-day treatment periods separated by a 7–10-day washout/restabilization period; and an end-of-study visit approximately 2 weeks after completing the second treatment period (Figure 1). Each treatment period consisted of 2 days at home and 4–6 days in a clinical research unit affiliated with each participating center. Eligible subjects were individually stabilized to an EC-bicarbonate-buffered PERT dose (maximum lipase dose of 2500 units/kg/meal) at home during the dose-stabilization period. A controlled high-fat diet (~2 g fat/kg/day) was begun and continued throughout the study. Each subject was treated with their established, stabilized lipase dose during subsequent active treatment periods. A blinded randomization list was prepared by a third party, linking kit number to treatment sequence. As the subjects were enrolled into the study, they were assigned the next available kit from the randomization list. Subjects were randomly assigned 1:1 to receive either active treatment or matching placebo during treatment period one and then crossed over to the alternate treatment during treatment period two. This allowed subjects to serve as their own controls. Information regarding study drug taken, concomitant medications and food intake during at-home periods, stool frequency and stool characteristics were recorded in subject diaries. Adverse event information was collected during each study visit. An Institutional Review Board at each study site approved the study protocol. Written informed consent (or assent) was obtained from all subjects or their parents or guardians prior to initiation of study-related procedures.

Children (aged 7 to <18 years) and adults with a confirmed diagnosis of CF, EPI (fecal elastase ≤ 100 μg/g stool), and currently receiving PERT were enrolled. An additional inclusion criterion was 'adequate nutritional status' defined as BMI ≥ fifth percentile for 7–20 year olds, BMI ≥ 16.0 for females >20 years old, or BMI ≥ 16.5 for males >20 years old. Subjects were excluded if they had evidence of other major organ diseases or syndromes that affect digestion or absorption (such as diabetes, liver
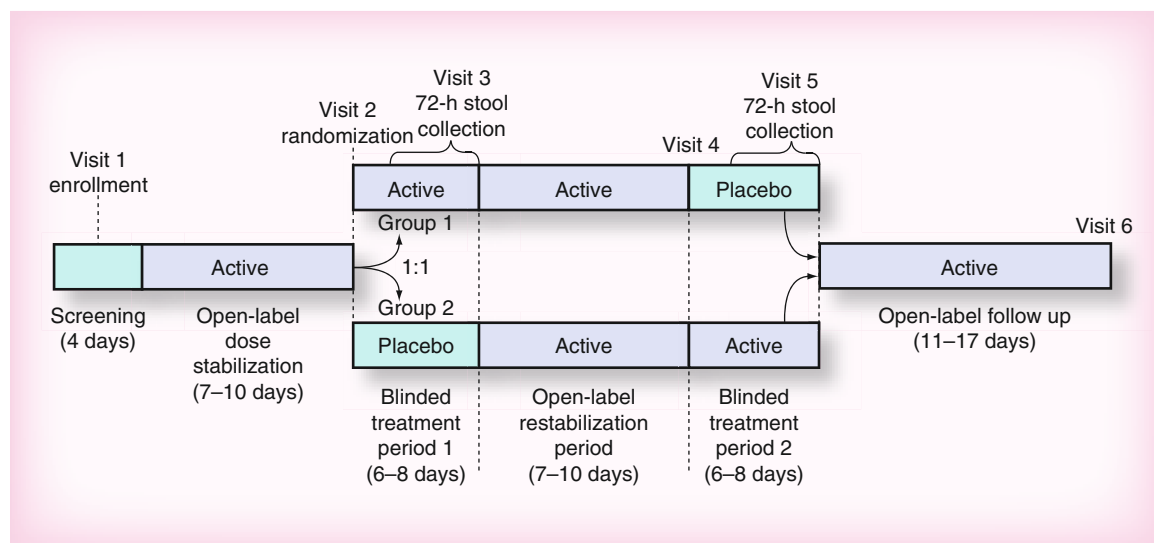

Figure 1. Randomized, double-blind, cross-over study design. Cystic fibrosis subjects were screened for eligibility over a 4-day period. Subjects began a controlled high-fat diet (~2 g/kg/day) and were stabilized on an enteric-coated, bicarbonate-buffered pancreatic enzyme replacement therapy product (active treatment) for 7–10 days, after which they were randomized 1:1 to receive blinded active treatment (Group 1) or placebo (Group 2) for 6–8 days. All subjects then received active treatment open-label for 7–10 days, after which Group 1 subjects received placebo and Group 2 subjects received active treatment for 6–8 days under blinded conditions. 72-h stool collections were performed during the blinded treatment periods. The high-fat diet was continued throughout the study. All subjects received open-label active treatment during the follow-up period.

disease, intestinal obstruction syndrome, inflammatory bowel disease or pancreatitis), a contraindication to porcine pancreatic enzymes, or acute treatment with systemic antibiotics within a 2 week period prior to screening.

Active study drug consisted of an EC-bicarbonate-buffered PERT microsphere formulation of pancrelipase (lipase, amylase and protease) in capsules filled to the 100% lipase label claim of 16,000 US Pharmacopeia units of lipase per capsule. The placebo contained inactive ingredients, and was encapsulated identically to active study drug to maintain blinding.

The controlled high-fat diet (~2 g fat/kg/day) contained approximately 45% calories as fat, 20% calories as protein and 35% calories as carbohydrate. Food intake was recorded in subject diaries during at-home periods and in the subject's records by research study staff during in-hospital periods. Subject food records during the in-hospital period were used for analysis of nutrient intake. Analysis of the food records was performed at the Nutrition Coordinating Center (University of Minnesota School of Public Health, MN, USA) using the Nutrition Data System for Research 2007 dietary analysis program (Version 9.0).

Stool collections aided by ingested dye markers were conducted during the two treatment periods for nutrient analyses (see [8] for detailed methodology). On day 3 and 6 of blinded treatment, the study drug was administered with breakfast, along with a stool dye marker (FD&C Blue Dye #2; 2 × 250 mg capsules). All stools passed after the appearance of the first dye marker up to and including the appearance of the second dye marker were collected. This timed stool collection period is often referred to as a 72-h stool collection. All collections were performed under supervision in a clinical research unit. The 72-h stool collection was weighed, and analyzed for fat and nitrogen content using NMR spectroscopy in a central laboratory (Mayo Clinical Trial Services, Rochester, MN, USA).

All subjects who completed both blinded treatment periods with adequate 72-h stool collection were included in efficacy analyses. All subjects who received at least one dose of study drug were included in safety analyses. The primary efficacy end point was the absolute difference in the coefficient of fat absorption (CFA) between active treatment and placebo, which was calculated from the 72-h stool collection and dietary records and defined as:

$$\left(\frac{\left[\begin{array}{c}\text{total fat intake(g/day)} - \\ \text{total fat excreted(g/day)}\end{array}\right]}{[\text{total fat intake(g/day)}]}\right) \times 100$$

Analysis of the absolute difference in the mean CFA during active treatment and placebo was performed using a mixed-model analysis of variance with fixed effects for age group, treatment sequence, treatment group, period, age × sequence interaction, age × treatment interaction and a random effect for subject within age × sequence. A sample size of 20 subjects was estimated to provide 90% power to detect an absolute difference in CFA of 30% between active treatment and placebo with a significance level of 0.05. Comparisons of treatment benefit within each age group were performed secondarily using least squares means, and the estimates of the treatment contrasts, associated p-values, and 95% confidence intervals were derived.

Using the same model, a comparison between treatment with active versus placebo with regards to the absolute difference in the coefficient of nitrogen absorption (CNA), the difference in stool frequency (bowel movements) and the difference in stool weight were analyzed as secondary efficacy end points. CNA was calculated from the 72-h stool collection and dietary records and was defined as:

$$\left(\frac{\left[\begin{array}{c}\text{total nitrogen intake(g/day)} - \\ \text{total nitrogen excreted(g/day)}\end{array}\right]}{[\text{total nitrogen intake (g/day)}]}\right) \times 100$$

Results

Out of the 29 subjects with CF who signed informed consent or assent (14 children and 15 adults), 24 (11 children, 13 adults) were randomized to receive the study drug at visit two (Table 1), and 21 (ten children, 11 adults) completed the study. Two subjects (one adult and one child) discontinued due to an adverse event during the placebo period. One adult subject discontinued due to inadequate stool collection during the placebo period. Mean calculated lipase dose for all subjects (US Pharmacopeia lipase units/kg body weight/meal) were 1406, 1557 and 1565 during dose stabilization, washout/restabilization, and treatment periods, respectively. No significant difference was noted for mean fat and protein intake during the 72-h stool collection period among subjects receiving active treatment versus placebo. Mean fat intake was 109 ± 30 and 114 ± 39 g/day ± SD during active and placebo treatment, respectively (p = 0.23). Mean protein intake was 109 ± 33 and 107 ± 31 g/day ± SD during active and placebo treatment, respectively (p = 0.54).

Overall, there was a statistically significant improvement in both fat and nitrogen absorption for active treatment over placebo treatment (Table 2). Mean CFA was 82.5% during active treatment versus 46.3% during placebo treatment, an absolute difference of 36.2 representing a 78.2% improvement for active treatment over placebo (p < 0.001). Mean CNA was 79.0% during active treatment versus 47.2% during placebo treatment, an absolute difference of 31.8%, representing a 67.4%

Table 1. Subject characteristics at randomization.										
Group	**Age (years)**		**Sex (n)**		**Race (n)**		**Height (cm)**		**Weight (kg)**	
	Range	**Mean ± SD**	**Females**	**Males**	**Caucasian**	**Black**	**Range**	**Mean ± SD**	**Range**	**Mean ± SD**
Children[†] (n = 11)	8–17	11.8 ± 2.96	3	8	11	0	126.0–164.5	144.9 ± 12.88	27.5–60.5	40.2 ± 11.77
Adults[‡] (n = 13)	18–43	26.5 ± 7.40	3	10	11	2	155.0–178.0	166.4 ± 7.29	45.0–66.8	58.8 ± 7.60
Total (n = 24)	8–43	19.8 ± 9.41	6	18	22	2	126.0–178.0	156.5 ± 14.81	27.5–66.8	50.3 ± 13.40
[†]Aged 7–17 years.										
[‡]Aged ≥ 18 years.										

relative improvement for active treatment over placebo (p < 0.001). Differences in CFA and CNA in favor of active treatment over placebo remained significant when comparing treatments within age subgroups (Table 2).

Subjects experienced statistically significant decreases in mean stool frequency (bowel movements) and mean stool weight over the 72-h stool collection period during active treatment compared with placebo treatment (Table 2). Overall, the number of bowel movements decreased 40% (p < 0.001) and mean stool weight decreased by 50% (p < 0.001; Table 2).

The incidence of treatment-emergent adverse events (regardless of causality) was similar during active treatment (76%) and placebo treatment (71%). The most common adverse events were gastrointestinal complaints, which were reported more commonly during placebo treatment (67%) than during active treatment (43%). The type and incidence of adverse events were similar in children and adults. All adverse events were assessed as mild or moderate in severity. Two subjects discontinued the study during placebo-treatment: an 18 year-old male due to decreased weight and an 11 year-old male due to increased laboratory values for liver enzymes and hepatic steatosis. There were no other clinically meaningful adverse trends in clinical laboratory parameters, vital sign assessments or physical examination findings.

Discussion

Good nutrition is critical to the survival and well-being of patients with CF. Treatment of EPI through the

Table 2. Treatment effects for subjects completing both treatment periods.			
Group	**Active Treatment[†] (%)**	**Placebo Treatment[†] (%)**	**Difference (% ± 95% CI)***
Coefficient of fat absorption			
Overall (n = 21)	82.5	46.3	36.2 ± 8.4
Children (n = 10)	80.8	45.8	35.0 ± 12.1
Adults (n = 11)	84.1	46.8	37.3 ± 11.5
Coefficient of nitrogen absorption			
Overall (n = 21)	79.0	47.2	31.8 ± 5.7
Children (n = 10)	78.4	43.8	34.6 ± 10.0
Adults (n = 11)	79.5	50.5	29.0 ± 7.8
Stool Frequency (bowel movements/72 h)			
Overall (n = 21)	6.1	10.1	-4.0 ± 1.6
Children (n = 10)	5.6	9.4	-3.8 ± 2.3**
Adults (n = 11)	6.6	10.8	-4.2 ± 2.2
Stool Weight (g/72 h)			
Overall (n = 21)	655.9	1308.5	-652.6 ± 160.8
Children (n = 10)	507.1	1086.2	-579.1 ± 232.5
Adults (n = 11)	804.7	1530.8	-726.1 ± 220.0
*p < 0.001 except where noted; **p < 0.01.			
[†]Least square means values.			

administration of exogenous pancreatic enzymes allows patients to better digest and subsequently absorb dietary nutrients; particularly fats, proteins, carbohydrates and fat-soluble vitamins. PERT addresses the significant malabsorption of these nutrients that occurs as a consequence of EPI [3]. Based on fat-balance studies measuring fat ingestion and fecal fat, the majority of people with CF and untreated EPI absorb <50% of ingested fat [9]. With EC-PERT, fat-balance studies that have not selected for responders demonstrate that the majority of people with CF and EPI can absorb >80% of ingested fat [10–13]. Healthy people without EPI absorb >90% [9]. The results of the current double-blind, placebo-controlled, cross-over study substantiate these observations, in that 46.4% of ingested fat was absorbed with placebo treatment, while 82.5% of ingested fat was absorbed with active treatment. Not only does active treatment with EC bicarbonate-buffered PERT result in a CFA >80%, but the absolute difference of 36.2% between placebo and active treatment exceeds the threshold difference of 30% that the FDA considers to be a benchmark for clinical effectiveness of PERT (see [8]). Additionally, in this study, treatment with EC-bicarbonate buffered PERT resulted in a significant decrease in the number of bowel movements and stool weight compared with placebo.

In addition to decreased pancreatic enzyme secretion, people with CF typically exhibit decreased pancreatic bicarbonate secretion and reduced intestinal tract pH, mostly affecting the duodenum [14]. Reduced pH can potentially inhibit endogenous as well as replacement enzyme activity, which is optimal at a neutral to basic pH [3]. *In vitro* lipase activity of several PERT formulations has been shown to decrease by 50% or more between pH 5.0 and 5.5, with EC formulations exhibiting minimal lipase activity below pH 5.0 [15]. The mean postprandial intraluminal pH in the distal duodenum of people with CF-associated EPI has been reported to be below 5.0, with individual values frequently less than 4.0 [16]. It has been suggested that this acidic environment may result in reduced release of enzymes as well as irreversible inactivation of lipase from EC-PERT products [3]. This may explain why some CF patients take higher than recommended amounts of a PERT product to control steatorrhea and to alleviate digestive symptoms. The US Cystic Fibrosis Foundation recommends no more than 2500 lipase units/kg of body weight/meal to avoid the development of fibrosing colonopathy [17,18]. The most recent data from the US Cystic Fibrosis Foundation Patient Registry reveals an average lipase dose of 1920 units/kg/meal for patients aged 2–19 years, and 1700 units/kg/meal for patients 20 years of age and older [2]. In this study of a bicarbonate-buffered PERT product, mean lipase doses during the blinded treatment periods and restabilization period were less than 1600 units/kg/meal.

Given that the optimal pH for maximal lipase activity is in the range of 8–9, it is hypothesized that a bicarbonate-buffered PERT product creates a microenvironment surrounding the microspheres for optimized activation of lipase in the duodenum and jejunum. This may result in the ability to administer lower doses of enzymes, thus avoiding gastrointestinal complications associated with higher enzyme doses. Another advantage would be reduction in treatment burden; fewer capsules would be required with each meal. Titration to the lowest effective lipase dose was not the subject of this study. However, a previous report of treatment with EC-bicarbonate-buffered PERT demonstrated that EC-bicarbonate-buffered PERT was significantly more effective than EC-PERT without bicarbonate in reducing steatorrhea in CF subjects when administered at equivalent doses (average 1145–1158 units/kg/meal or 4315–4366 units/kg/day) [6]. Since that study was performed with unapproved PERT products, and given the availability of a number of FDA-approved formulations of PERT products [19], additional studies should be considered to determine if any nonbuffered EC-PERT product would have comparable efficacy to an EC-bicarbonate-buffered PERT product.

Future perspective

EPI is a developmental event in CF that is present at birth or shortly thereafter in the majority of people with CF [1]. Proper nutrition management of newborns with CF is critical to their healthy development, and for this reason, management of CF-associated EPI will remain an important component of CF care, even if/when use of agents mitigating the primary CF defect becomes widespread [20]. Thus, PERT will continue to be an important therapy for nearly all people with CF.

More work needs to be done to optimize therapy with PERT products, including determining how to better titrate enzyme dosing (to reduce treatment burden), developing pediatric formulations that are easier to administer to infants and toddlers (e.g., noncapsule formulations) and developing formulations to be used with continuous feeding (e.g., via gastrostomy tube).

A head-to-head comparison of the safety and efficacy of this bicarbonate-buffered PERT product with another FDA-approved nonbuffered PERT product would be of particular interest.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- The efficacy and safety of a unique enteric-coated bicarbonate-buffered pancreatic enzyme replacement therapy (PERTZYE®/PANCRECARB®) was studied in 24 children and adults with cystic fibrosis and exocrine pancreatic insufficiency using a multicenter, prospective, randomized, double-blind, placebo-controlled, cross-over design.
- Active treatment compared with placebo resulted in a significant mean improvement in fat and nitrogen absorption, and a decrease in the number of bowel movements and stool weight ($p < 0.001$ for all). Treatment-emergent adverse events were mild-to-moderate, most commonly gastrointestinal-associated, and not significantly different between treatments.
- The results of this study support the use of enteric-coated bicarbonate-buffered pancreatic enzyme replacement therapy as an effective treatment for exocrine pancreatic insufficiency in children and adults with cystic fibrosis.

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Papers of special note have been highlighted as:
- ■   of interest
- ■■   of considerable interest

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■   **Provides an overview of cystic fibrosis (CF), including gastrointestinal manifestations, for the reader who is unfamiliar with this disease.**

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