Efficacy of a Novel Pancreatic Enzyme Product, EUR-1008 (Zenpep), in Patients With Exocrine Pancreatic Insufficiency Due to Chronic Pancreatitis

Phillip P. Toskes, MD, Angelo Secci, MD,† and Ruth Thieroff-Ekerdt, MD†*
for the ZENPEP Study Group

Objectives: EUR-1008 (ZENPEP® [pancrelipase] Delayed-Release Capsules)[a] delayed-release capsules is a novel, enteric-coated, porcine-derived pancreatic enzyme product. This study evaluated the efficacy and safety of 2 doses of ZENPEP in patients with chronic pancreatitis (CP) and exocrine pancreatic insufficiency (EPI).

Methods: The effect of ZENPEP on the coefficient of fat absorption (CFA) was investigated in a randomized, double-blind, dose-response, crossover study with placebo run-in (7–9 days) and 2 treatment periods (9–11 days) composed of a high dose (7 × 20,000 lipase units per day) and a low dose (7 × 5000 lipase units per day).

Results: Mean CFA was significantly higher with low- (88.9%) and high-dose (89.9%) ZENPEP versus placebo run-in (82%; $P < 0.001$; n = 72) with no difference between doses ($P = 0.228$, primary end point). In patients with baseline CFA less than 90% (n = 33), the high dose was significantly more effective (CFA: 84.1%) than the low dose (CFA: 81.1%; $P < 0.001$). Post hoc analysis revealed an increase in treatment effect with more severe EPI. Coefficient of nitrogen absorption ($P < 0.001$), body weight ($P \leq 0.021$), and body mass index ($P \leq 0.020$) also increased significantly with both doses compared with baseline. Percentage of days with EPI symptoms decreased with both doses.

Conclusions: Our findings suggest that CP patients with EPI benefit from a low dose of ZENPEP, whereas the high dose might be needed for patients with more severe EPI.

Key Words: chronic pancreatitis, exocrine insufficiency, pancreatic enzyme replacement therapy, coefficient of fat absorption, crossover trial

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Chronic pancreatitis (CP) is an inflammatory process leading to progressive and irreversible damage of the pancreas.[1] In the United States, CP is estimated to affect 5 to 24 million people.[2] Among patients with CP, approximately 40% to 50% develop exocrine pancreatic insufficiency (EPI).[3,4] Exocrine pancreatic insufficiency is a functional deficiency of the pancreas with decreased secretion of pancreatic enzymes resulting in maldigestion and malabsorption.[5] Clinical symptoms include diarrhea, steatorrhea, and weight loss.

Pancreatic enzyme replacement therapy with exogenous porcine-derived pancreatic enzyme preparations (PEPs) has been a cornerstone of EPI therapy for decades.[6] ZENPEP® (pancrelipase) delayed-release capsules is a novel porcine-derived pancreatic enzyme product developed to be compliant with new US Food and Drug Administration (FDA) requirements. ZENPEP capsules, available in 4 dosing strengths (5000, 10,000, 15,000, and 20,000 USP lipase units; Eurand, Yardley, Pa), contain enteric-coated beads and are manufactured to 100% of label lipase claim with no overage.

The efficacy and safety of ZENPEP for improving steatorrhea in patients with EPI associated with cystic fibrosis (CF) have previously been reported.[7] The current study, which is the first report of ZENPEP treatment of patients with EPI due to CP, was designed to investigate the efficacy and safety of 2 doses of ZENPEP in this population. The higher ZENPEP dose used in the study (140,000 lipase units per day) was selected to be within the range of published dosing recommendations, whereas the lower dose (1/4 of the higher dose) was expected to have no or little effect on steatorrhea.

MATERIALS AND METHODS

Study Design and Treatment

This was a randomized, double-blind, dose-response, crossover study of ZENPEP. Nineteen sites (10 in the United States, 5 in Ukraine, and 4 in Italy) enrolled 82 patients between January 2008 and March 2009. ZENPEP was administered at a fixed daily dosage of 7 capsules per day, distributed according to the estimated fat content of the meals (eg, 2 capsules with meals, 1 capsule with snacks). Patients administered the low dose of ZENPEP ("ZENPEP low"), seven 5000-USP lipase unit capsules, received a total daily dose of 35,000 USP lipase units. Patients administered the high dose of ZENPEP ("ZENPEP high"), seven 20,000-USP lipase unit capsules, received a total daily dose of 140,000 lipase units.

Study Conduct

After providing informed consent and undergoing screening, eligible patients were administered placebo capsules and entered the placebo baseline run-in phase (4-day ambulatory treatment). On day 5, they were hospitalized for 3 to 5 days for the baseline 72-hour measure of coefficient of fat absorption (CFA). The in-hospital diet contained a minimum of 100 g of fat daily. Patients were randomized to 1 of 2 active treatment crossover phases (a "high/low" or "low/high" dose sequence) and entered a 6-day ambulatory treatment period at home. Patients followed a diet prescribed by the site dietician and recorded data on study drug consumption, diet, clinical signs and symptoms, nonstudy drugs taken, and adverse events (AEs) in a patient diary. After 6 days, patients were hospitalized for 3 to 5 days to perform 72-hour CFA testing as described for the

From the *Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Florida, Gainesville, FL; and †Eurand Pharmaceuticals, Inc, Yardley, PA.
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Reprints: Phillip P. Toskes, MD, Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Florida, PO Box 100214, Gainesville, FL 32610-0214 (e-mail: toskepp@medicine.ufl.ed).
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[a]ZENPEP® (pancrelipase) Delayed—Release Capsules, Eurand Pharmaceuticals, Inc, Yardley, PA

placebo run-in period. Patients were then crossed over to the other dose and repeated the same treatment sequence (Fig. 1).

Subject Selection Criteria

Eligible patients were older than 18 years with a diagnosis of CP by medical history, preferably supported by at least one of the following imaging tests: abnormal endoscopic retrograde cholangio-pancreatography Cambridge Class 4, abnormal computed tomographic scan (dilated main pancreatic duct, atrophy of the pancreas, or calcification), abnormal ultrasound, or endoscopic ultrasound with 5 or more abnormalities noted. Patients with partial or distal pancreatic resection (not due to cancer) were also eligible. Exocrine pancreatic insufficiency was documented by fecal elastase (FE1) of 100 μg/g of stool or less (Pancreatic Elastase 1; Genova Diagnostics, Asheville, NC) performed at the screening visit. Patients with a history of CF, excessive alcoholism, drug abuse, uncontrolled diabetes, acute pancreatitis, noncutaneous malignancy, or human immunodeficiency virus infection were excluded.

Concomitant Medications

Unlike other studies of pancreatic enzyme replacement therapy in EPI, a considerable effort was made to exclude medications that could affect the response to PEPs. At the start of the placebo treatment, patients discontinued all pancreatic enzyme products. Medications excluded from the study were antacids, anticholinergics, antispasmodics, octreotide, human growth hormone, motility agents (eg, metoclopramide and macrolides), agents for gastric ulcers (eg, misoprostol), proton pump inhibitors, H_2 blockers, sucralfate, synthetic fat substitutes (eg, olestra), or fat-blocking nutritional supplements and laxatives (including mineral oil and castor oil).

Efficacy and Safety Assessments

In-hospital stool sampling for the 72-hour CFA was performed after the placebo run-in phase and at the completion of the 2 ZENPEP dosing periods. Indigo dye marked the beginning and end of the stool collection period after which patients were discharged and entered the ambulatory treatment phase at home. The CFA, expressed as a percentage, was defined as follows: [(fat intake − fat excretion)/fat intake] × 100. Safety and tolerability were assessed from AE reporting, clinical laboratory parameters, physical examination, and vital signs.

Statistical Methods

Data were analyzed for the full analysis set (FAS) consisting all patients who received at least 1 dose of study medication and a modified full analysis set (MFAS) consisting of patients in the FAS whose placebo baseline CFA was determined to be 90% or lower. Hypothesis testing was performed at the $\alpha = 0.05$ level (2-sided) when comparing treatments. Statistical power was calculated on the absolute percentage difference in CFA between ZENPEP low and ZENPEP high (primary end point). On the basis of data from CF patients, an SD of 20% was assumed for CFA. Using a 2-sided paired *t* test with type 1 error rate $\alpha = 0.05$ and power of 85%, a sample size of 60 evaluable patients was sufficient to detect a statistically significant mean absolute difference for a true underlying difference in CFA of 11.1%. Taking into account the likelihood that repeat CFA values in a subject were correlated, the true difference for which power was 85% would be lower than 11.1%; for example, a correlation of 0.5 would correspond to a true difference of 7.9%.

The primary end point was the difference in CFA for patients treated with ZENPEP high versus ZENPEP low analyzed by means of an analysis of covariance model. The model included patient nested within sequence as random effect, treatment period and sequence as fixed effects, and placebo baseline CFA value as covariate. The least squares (LS) mean from this model were used to estimate the treatment effect.

Secondary end points included the difference in CFA for ZENPEP high and ZENPEP low versus placebo baseline, change in coefficient of nitrogen absorption (CNA) from placebo baseline, and change in weight and body mass index (BMI) from placebo baseline. Exploratory end points included change in serum cholesterol and fat-soluble vitamins (A, E, and K) from baseline and between doses. The incidence of clinical signs (stool frequency, consistency, and oil/blood in stool) and patient-reported symptoms of malabsorption because of EPI (intestinal bloating, pain, and flatulence) during each treatment period was summarized using descriptive statistics.

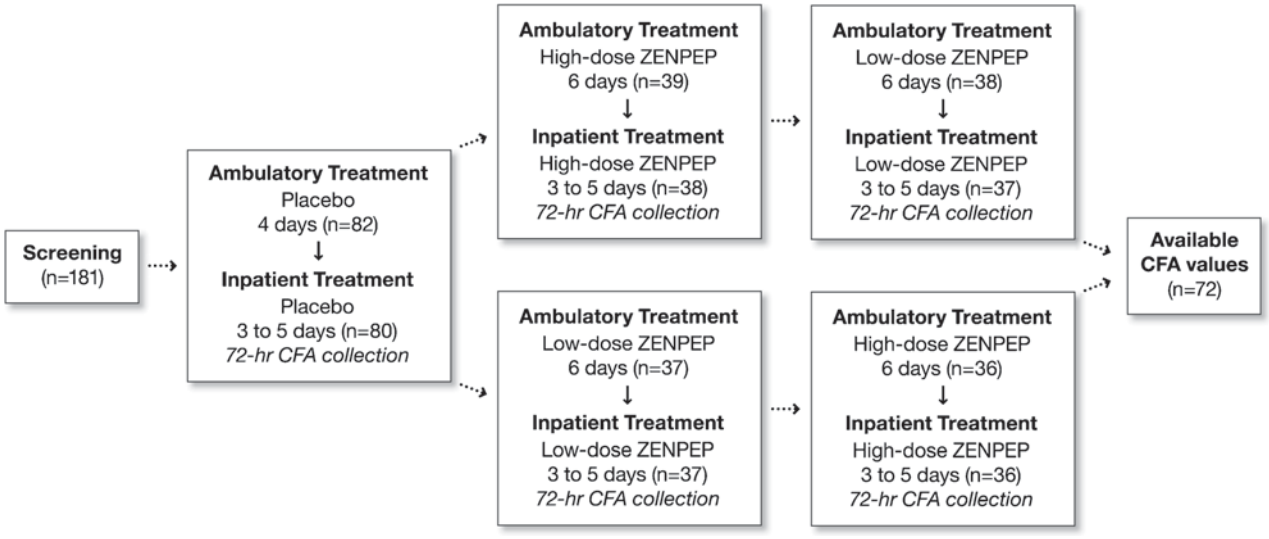

FIGURE 1. Study design. After screening, patients were administered placebo capsules at home for 4 days followed by in-hospital baseline stool collection (72 hours). Patients were randomized to a low-high or high-low dosing sequence with ZENPEP, each consisting of a treatment period performed at home and followed by in-hospital 72-hour stool collection.

TABLE 1. Demographics

Demographic Variable	Placebo Run-In	ZENPEP High/Low	ZENPEP Low/High
n	82	39	37
Sex, n (%)			
Male	53 (64.63)	22 (56.41)	28 (75.68)
Female	29 (35.37)	17 (43.59)	9 (24.32)
Ethnic origin, n (%)	71 (86.59)	34 (87.18)	32 (86.49)
White	9 (10.98)	5 (12.82)	3 (8.11)
Black	1 (1.22)	0 (0.00)	1 (2.70)
Hispanic	1 (1.22)	0 (0.00)	1 (2.70)
Age, mean (SD), yr	51.91 (12.08)	51.87 (12.02)	52.70 (12.20)
Weight, mean (SD), kg	68.75 (14.12)	70.04 (15.00)	68.69 (13.44)
BMI, mean (SD), kg/m^2	23.36 (4.44)	24.15 (4.43)	22.97 (4.48)

A post hoc analysis evaluated the absolute and percent change in CFA from placebo baseline as a function of baseline CFA range (<65%, 65% to <75%, 75% to <85%, ≥85%).

RESULTS

Study Population

Eighty-two patients (FAS) were enrolled and received placebo during the placebo run-in phase. Seventy-six patients were randomized to treatment with ZENPEP high/low (n = 39) or low/high (n = 37) and 72 patients provided complete CFA data. The MFAS comprised 34 patients with a placebo baseline CFA of 90% or lower (n = 22 in the high/low group and n = 12 in the low/high group), and 33 of these patients provided complete CFA data.

Baseline Demographics and Disease History

Most patients were white (87%), and the mean age was 52 years (range, 22–82 years). More men than women were enrolled in the study (64.6% vs 35.4%, respectively), and there were more males than females (75.7% vs 24.3%) for the low/high–dose sequence group (Table 1). Of 82 patients, 93.9% (n = 77) had a diagnosis of CP that was also supported by at least 1 additional diagnostic test including endoscopic retrograde cholangiopancreatography, computed tomographic scan, ultrasound or endoscopic ultrasound, and radiography.

Efficacy Results

Mean CFA measured at the end of the placebo run-in phase was 81.7% (Table 2). The primary end point comparing the difference in LS mean between the 2 ZENPEP doses was not statistically significant ($P = 0.228$). Coefficient of fat absorption was significantly higher after treatment with both ZENPEP doses. The mean CFA observed with ZENPEP low was 88.9% (95% confidence interval, 85.95%–91.79%, $P < 0.001$) and 89.9% with ZENPEP high (95% CI, 87.80%–91.92%, $P < 0.001$) compared with placebo run-in (81.7%; 95% CI, 76.48%–86.88%). To evaluate the presence of a country effect (United States, Italy, and Ukraine) for the primary efficacy variable, the country was further included in the analysis of covariance model as covariate and was found to be nonsignificant. Coefficient of nitrogen absorption was also significantly higher after both ZENPEP treatments (84.1% and 85.4% for low and high, respectively, $P < 0.001$) versus a placebo run-in value of 78.1%.

The mean body weight and BMI increased significantly after treatment with both ZENPEP doses when compared with placebo run-in values. Among the subset of patients who provided full data on weight and BMI, treatment with ZENPEP low was associated with a weight gain of 0.38 kg (95% CI, 0.06–0.70 kg, $P = 0.021$) and treatment with ZENPEP high was associated with a weight gain of 0.50 kg (95% CI, 0.15–0.85 kg,

TABLE 2. Coefficients of Fat and Nitrogen Absorption for Patients at Placebo Run-In and After Treatment With ZENPEP

Study Parameter	Placebo Run-In	ZENPEP Low	ZENPEP High
CFA			
n	72	72	72
Mean % (SD)	81.68 (22.13)	88.87 (12.44)	89.86 (8.77)
95% CI on mean	76.48–86.88	85.95–91.79	87.80–91.92
Mean change vs placebo run-in (SD)	—	7.19 (14.49)	8.18 (17.35)
95% CI on mean change	—	3.78–10.59	4.10–12.26
P	—	<0.001	<0.001
CFA for MFAS			
n	33	33	33
Mean % (SD)	65.04 (23.57)	81.11 (14.78)	84.07 (9.01)
95% CI on mean	56.68–73.39	75.87–86.35	80.87–87.26
Mean change vs placebo run-in (SD)	—	16.07 (17.49)	19.03 (20.47)
95% CI on mean change	—	9.87–22.27	11.77–26.29
P	—	<0.001	<0.001
CNA			
n	76	74*	75*
Mean % (SD)	78.05 (18.64)	84.11 (11.67)	85.44 (8.66)
Mean change vs placebo run-in (SD)	—	5.33 (10.38)	7.62 (15.55)
95% CI on mean change	—	2.91–7.75	4.02–11.23
P	—	<0.001	<0.001

*Full CNA data not available.

$P = 0.006$). Similarly, BMI increased significantly from placebo run-in in patients after treatment with ZENPEP low (0.13 kg/m^2; 95% CI, 0.02–0.23 kg/m^2, $P = 0.020$) and treatment with ZENPEP high (0.16 kg/m^2; 95% CI, 0.05–0.27 kg/m^2, $P = 0.007$). Results for secondary measurements of lipid levels showed significantly higher HDL-C levels with both doses of ZENPEP compared with placebo run-in ($P < 0.001$), whereas LDL-C levels remained unchanged. In addition, there were no significant changes in fat-soluble vitamins (A, E, and K) after ZENPEP treatment.

Efficacy as a Function of Baseline CFA

The MFAS was predefined as patients with placebo run-in CFA of 90% or lower; this population (n = 33) had a mean CFA at placebo run-in of 65%. Comparison of the ZENPEP low versus ZENPEP high in the MFAS showed a statistically significant difference between the LS means (80.8% vs 84.4%, respectively, $P = 0.034$) in favor of the higher dose. The CFA in this subgroup also increased significantly from placebo run-in after treatment with both ZENPEP low and ZENPEP high, with a mean change from placebo run-in of 16.07 (95% CI, 9.87–22.27, $P < 0.001$) and 19.03 (95% CI, 11.77–26.29, $P < 0.001$), respectively. In a post hoc analysis, patients were stratified by severity of steatorrhea at placebo run-in, as measured by CFA values (<65%, 65% to <75%, 75% to <85%, and >85%,). Improvements in the CFA percentage were observed to increase with decreasing CFA at placebo run-in for both ZENPEP low and high (Fig. 2). Treatment with ZENPEP high was associated with greater increases in CFA compared with ZENPEP low in subjects with severe steatorrhea (CFA <65%; 36.8 with ZENPEP high and 27.1 with ZENPEP low). Although patient numbers in the different CFA ranges were deemed to be too small to allow for formal statistical testing of treatment difference, improvements in CFA from placebo run-in increased with decreasing baseline CFA for both low- and high-dose ZENPEP.

Symptoms and Stool Characteristics

Table 3 summarizes the mean number of days of patient-reported symptoms associated with EPI and stool characteristics. The mean percentage of days with any symptoms during treatment with the 2 ZENPEP dose levels was lower (53.9% and 53.0% for low and high, respectively) compared with placebo run-in (67.6%). Similarly, the mean percentage of days with abdominal pain was 28.1% and 29.0% for ZENPEP low and ZENPEP high compared with 39.8% during the placebo run-in period. The percent of days with flatulence and bloating was similar after treatment with both ZENPEP doses. The mean percentage of days with formed/normal stools during treatment with the 2 ZENPEP doses was higher than that reported during the placebo run-in period (89.7% and 89.9% for low and high, respectively) compared with 92.1% during the placebo run-in period. Similarly, the mean percentage of days with oil/grease in stool was lower in both the ZENPEP doses compared with placebo run-in. Six patients reported blood in stools. Of these 6 patients, 3 had 3 or more stools with blood occurring from 1 to 3 consecutive study days. The other 3 patients had only 1 stool with blood during the entire study. The consistency of half of all stools with blood was described as either "hard" or "formed/normal." The consistency of the other half of stools with blood was described as "soft." The limited occurrence of blood in the

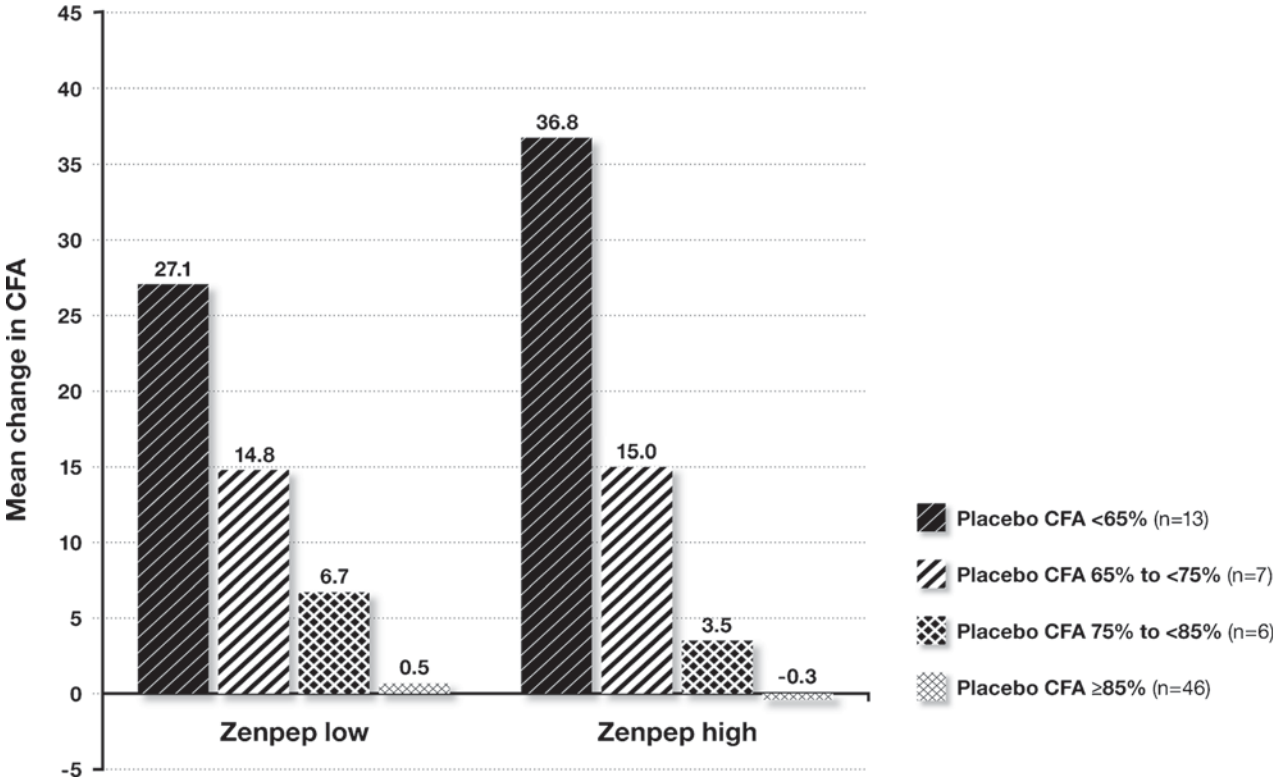

FIGURE 2. Mean change in CFA percentage in patients stratified by severity of steatorrhea at placebo run-in. Improvements in CFA from placebo run-in increased with decreasing baseline CFA for both low- and high-dose ZENPEP. Treatment with high-dose ZENPEP was associated with greater increases in CFA compared with low-dose ZENPEP in patients with severe steatorrhea (CFA <65%).

TABLE 3. Signs and Symptoms of EPI at Placebo Run-In and After Treatment With ZENPEP Low or ZENPEP High*

Sign/Symptom	Placebo Run-In	ZENPEP Low	ZENPEP High
Percentage of days with symptoms, mean (SD)	67.62 (34.95)	53.94 (39.38)	52.99 (37.76)
Percentage of days with any abdominal pain, mean (SD)	39.81 (38.70)	28.06 (38.12)	28.97 (36.97)
Percentage of days with bloating, mean (SD)	40.05 (38.93)	33.31 (40.64)	31.75 (38.18)
Percentage of days with flatulence, mean (SD)	57.12 (36.97)	48.29 (39.50)	46.76 (37.44)
Percentage days with normal/formed stools, mean (SD)	30.33 (29.96)	45.01 (32.11)	44.26 (30.59)
Percentage days with oil/grease in stools, mean (SD)	17.13 (28.17)	9.37 (20.38)	9.27 (21.40)
Percentage days with blood in stool, mean (SD)	0.59 (4.30)	0.77 (3.52)	1.04 (3.24)

*Descriptive statistics only.

stools suggests that the blood most likely resulted from an external source to the intestinal mucosa (eg, skin irritation).

Safety Results

ZENPEP was well tolerated at both doses. Table 4 provides a summary of treatment-emergent AEs (TEAEs) by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs were reported by 35 patients (42.68%) during the placebo run-in phase, by 29 patients (39.19%) during treatment with ZENPEP low, and by 31 patients (41.33%) during treatment with ZENPEP high. The most common TEAEs were gastrointestinal disorders of which flatulence and abdominal pain were the most commonly reported. The next most commonly reported system organ class was nervous system disorders, which were reported in 5 patients (6.10%) during the placebo period, 4 patients (5.41%) with low dose, and 4 patients (5.33%) with high dose. Within the nervous system disorders, headache was reported most commonly in 3 patients (3.66%), 4 patients (5.41%), and 2 patients (2.67%) during placebo run-in, ZENPEP low, and ZENPEP high, respectively. Dizziness was reported in 2 patients (2.44%) during the placebo run-in period. Cognitive disorder was reported in 1 patient (1.33%) in the ZENPEP high treatment group in addition to hypoesthesia reported in 1 patient (1.33%) in the same treatment group. Investigator-suspected drug-related AEs were reported for 17 patients (20.73%) during the placebo run-in phase, 10 patients (13.51%) with ZENPEP low, and 7 patients (9.33%) with ZENPEP high treatment. Most drug-related AEs (85%) were mild or moderate in intensity across all treatment groups. Two patients in the placebo run-in phase and in each of the ZENPEP treatment groups experienced a serious AEs; none of these were considered drug-related. Three patients discontinued the study as a result of an AE (2 during the placebo run-in phase and 1 during ZENPEP high-dose); none of which were drug-related. There were no deaths reported during the study.

Laboratory testing (hematology, blood chemistry, and urinalysis) revealed no substantial differences in values for the placebo run-in and ZENPEP treatment phases. There were no reports of clinically significant elevations in serum and urinary uric acid levels.

DISCUSSION

ZENPEP is a novel FDA-approved pancreatic enzyme product indicated for the treatment of EPI due to CF and other conditions, adhering to new FDA guidelines on pancreatic enzyme products requiring 100% labeled lipase content and consistent

TABLE 4. Treatment-Emergent AEs

System Organ Class Preferred Term	Placebo Run-In	ZENPEP Low	ZENPEP High
n	82	74	75
Patients with TEAEs, n (%)	35 (42.68)	29 (39.19)	31 (41.33)
Patients with suspected drug related TEAEs, n (%)	17 (20.73)	10 (13.51)	7 (9.33)
Patients with SAEs, n (%)	2 (2.44)	2 (2.70)	2 (2.67)
Patients withdrawn because of TEAEs, n (%)	2 (2.44)	0 (0.00)	1 (1.33)
GI disorders, n (%)	28 (34.15)	20 (27.03)	23 (30.67)
Abdominal pain, n (%)	12 (14.63)	7 (9.46)	13 (17.33)
Constipation, n (%)	1 (1.22)	2 (2.70)	5 (6.67)
Diarrhea, n (%)	5 (6.10)	3 (4.05)	1 (1.33)
Dyspepsia, n (%)	2 (2.44)	1 (1.35)	1 (1.33)
Flatulence, n (%)	18 (21.95)	7 (9.46)	10 (13.33)
Nausea, n (%)	2 (2.44)	3 (4.05)	1 (1.33)
Vomiting, n (%)	3 (3.66)	1 (1.35)	2 (2.67)
Nervous system disorders, n (%)	5 (6.10)	4 (5.41)	4 (5.33)
Headache, n (%)	3 (3.66)	4 (5.41)	2 (2.67)
Dizziness, n (%)	2 (2.67)	0 (0.00)	0 (0.00)
Cognitive disorder, n (%)	0 (0.00)	0 (0.00)	1 (1.33)
Hypoesthesia, n (%)	0 (0.00)	0 (0.00)	1 (1.333)

SAE indicates serious adverse event.

stability and quality. The efficacy and safety of ZENPEP have been demonstrated in 2 clinical trials in adult and pediatric patients with EPI due to CF.

Here, we present data from a multinational, randomized, double-blind, dose-controlled crossover study of ZENPEP in patients with CP and EPI defined by FE of 100 μg or less per gram of stool. A mean CFA of 82% after 7 to 9 days of placebo treatment during the run-in phase indicated that patients, on average, had only mild to moderate EPI. The primary end point for this study, change in CFA for ZENPEP low versus ZENPEP high, did not reach statistical significance; however, treatment with ZENPEP at both doses was associated with significant improvements in fat absorption to near-normal levels when compared with placebo run-in.

Further analyses of dosing and disease severity indicated that treatment effects and differentiation between the low and high ZENPEP doses increased with more severe EPI. A predefined subgroup population (MFAS), which included patients with CFA of 90% or lower and comprised approximately half of the evaluable patients (33/72), had a placebo run-in mean CFA of 65%. In this patient population, the mean CFA after ZENPEP low and ZENPEP high was 80.8% and 84.4%, respectively, with a statistically significant difference between both doses.

Stratifying patients by CFA range at placebo run-in illustrated that treatment effects were larger as the baseline CFA values became lower. In patients with a placebo run-in CFA less than 65%, an increased benefit of the higher dose was evident (absolute change in CFA of 36.8 with ZENPEP high vs 27.1 with ZENPEP low). Both low- and high-dose regimens of ZENPEP were generally well tolerated.

There are few other published studies that have evaluated PEP treatment in patients with CP. Two formulations of pancreatin (Creon 10,000 lipase units as microspheres or minimicrospheres) were compared in a double-blind, randomized, crossover study of patients with CP.[8] Coefficient of fat absorption values reached approximately 80% after treatment with both formulations, and the study authors noted that FE values were less than 20 μg/g of stool in 89% of patients in their study, suggesting a population with severe EPI.[8] Safdi et al[9] reported results from a randomized, blinded, parallel group study in 26 patients comparing pancrelipase (Creon 10,000 lipase units) with placebo, showing a significant treatment effect. A new formulation of Creon containing 12,000 lipase units per capsule has recently been evaluated in a double-blind, randomized, placebo-controlled study enrolling patients with CP or pancreatic surgery and also demonstrated a significant treatment effect over placebo.[10]

Vecht et al[11] published the only other study we are aware of which compared 2 PEP dosing strengths in a controlled study evaluating treatment of EPI due to CP. Exocrine pancreatic insufficiency was confirmed by fecal fat excretion greater than 10 g/24 h in this small crossover study (N = 16) in which patients were treated with Pancrease 10,000 lipase units or 20,000 lipase units (3 times a day), plus a proton pump inhibitor. Patients improved significantly from a baseline CFA of 49% to 76% (low dose) and 75% (high dose) after treatment.[11] Scores reflecting abdominal symptoms and general well-being were similar for the 2 dosing groups.

The placebo run-in CFA in our study was notably higher than expected, and it suggests that FE as a diagnostic criterion for EPI in CP patients should be regarded as a qualifying rather than a quantifying biomarker for EPI. These data suggest that other baseline characteristics such as disease duration and clinical symptoms will need to be taken into account to assess EPI severity, even in the presence of a low FE level. Treatment with ZENPEP low (7 × 5000 lipase units per day) in this study was associated with significant improvements in CFA, CNA, and weight compared with placebo run-in, restoring fat absorption to a near-normal degree. Also, percent of days with symptoms, abdominal pain, flatulence, and bloating were similar after treatment with ZENPEP low and ZENPEP high.

Ours is the second study in addition to that of Vecht et al to demonstrate a potential benefit of low-dose PEP treatment in patients with mild to moderate EPI due to CP. Future studies of EPI in CP patients are needed to further evaluate the dose response relationship of PEP treatment in CP patients.

CONCLUSIONS

ZENPEP is an FDA-approved, enteric-coated, stable porcine-derived pancreatic enzyme replacement preparation with 100% of labeled lipase content without overage. Both high-dose and low-dose ZENPEP improved clinical parameters of protein and fat absorption as well as increased body weight and BMI and were well tolerated. These data suggest that patients with CP with less severe EPI could possibly be managed with a low-dose enzyme preparation, whereas patients with severe EPI would benefit from a higher dose.

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