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Original Article

EUR-1008 pancreatic enzyme replacement is safe and effective in patients with cystic fibrosis and pancreatic insufficiency☆

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Abstract

Background: EUR-1008 (Zenpep™ [pancrelipase]) is a new, enteric-coated, porcine-derived pancreatic enzyme product (PEP) developed for the treatment of cystic fibrosis (CF) patients with malabsorption associated with exocrine pancreatic insufficiency (EPI). Unlike currently marketed PEPs, EUR-1008 contains the label-claimed lipase content. Safety and efficacy were assessed in younger (<7 years) and older (≥7 years) CF patients with EPI.
Methods: Two multicenter studies were conducted: a randomized, double-blind, placebo-controlled, crossover trial in patients ≥7 years of age ($N=34$) and a supplemental, open-label study in children <7 years of age ($N=19$). Use of any medications altering gastric pH/motility was prohibited during the studies. Outcome measures in the randomized trial included changes in the coefficient of fat absorption (CFA), coefficient of nitrogen absorption (CNA), and signs/symptoms of malabsorption for EUR-1008 vs. placebo. Outcome measures in the supplemental study included safety and response (defined as no steatorrhea and no overt signs/symptoms of malabsorption) to EUR-1008 vs. previous enzyme treatment.
Results: In the randomized trial, EUR-1008 treatment compared to placebo resulted in a significantly higher mean CFA (88.3% vs. 62.8%, respectively) and CNA (87.2% vs. 65.7%, respectively) (both $p<0.001$) and reduced the incidence of malabsorption signs and symptoms in 32 evaluable patients. In the supplemental study, 11 of 19 patients met the criteria for responder with EUR-1008 at the end of the study vs. 10 of 19 patients at screening (previous PEP), and improvements in clinical symptoms were reported with EUR-1008 treatment. EUR-1008 was safe and well tolerated, and no serious drug-related AEs were reported in either study.
Conclusions: EUR-1008 was safe, well tolerated, and effective in CF patients of all ages with EPI-associated malabsorption in two clinical trials. Treatment led to clinically and statistically significant improvements in CFA and CNA in the randomized study, and control of malabsorption and clinical symptoms in both studies.

Keywords: Cystic fibrosis; Pancreatic insufficiency; Pancreatic enzyme replacement; Malabsorption; Pancrelipase; Overfill

☆ Clinical trials registration number for randomized study in patients ≥7 years of age: NCT00297167.

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1. Introduction

Exocrine pancreatic insufficiency (EPI) is defined as fecal elastase <100 μg/g in the stool [1], and occurs in approximately 85% of cystic fibrosis (CF) patients [2,3], resulting in impaired digestion and decreased absorption of nutrients [3]. Signs and symptoms of EPI include malabsorption, steatorrhea, bloating, pain, and flatus, which develop soon after birth. Poor nutritional status associated with untreated or insufficiently treated EPI impairs growth, compromises pulmonary outcomes, weakens immune response, and shortens the life expectancy of CF patients [4–11]. The use of oral pancreatic enzyme products (PEPs) significantly improves the nutritional status of CF patients, which is closely linked to improvements in lung function [4–11] as well as the increased life expectancy that has been achieved by CF patients over the previous decades [12,13]. Therefore, improving the nutritional status of patients with CF and EPI is a goal of treatment, and supplementation with PEPs at meals and snacks is the mainstay of therapy for EPI.

PEPs are typically a mixture of porcine-derived pancrelipase, which is a combination of three enzymes: lipase, amylase and protease. Current gastric acid-protected products are designed to release enzymes in the upper small intestine to aid digestion and improve nutrient absorption. Among currently marketed PEPs for EPI, great variability in the amount of enzymes included in each capsule has been noted [14–17], due in part to the manufacturer practice of overfilling capsules to account for enzyme degradation that occurs over the course of the product's shelf life. Variability in the product's enzyme content can lead to inconsistent therapeutic effects by either providing too much or too little of the required enzymes, which may lead to the suboptimal treatment of the patient's EPI. In addition, overfilled products may increase the risk of fibrosing colonopathy, which has been associated in some reports with long-term exposure to high-dose pancreatic enzyme replacement therapy [18–20]. Most PEPs were developed before current United States Food and Drug Administration (FDA) New Drug Approval (NDA) requirements were enacted [21]. The possible safety risk posed by high-dose enzyme therapy, particularly fibrosing colonopathy [18–20], in combination with the issue of enzyme overfill, recently prompted the FDA to require the manufacturers of PEPs to demonstrate drug efficacy and safety in randomized, placebo-controlled trials before approval [21]. Guidelines from the FDA now require that new PEPs be formulated to meet the label-claimed enzyme content and demonstrate safety and efficacy in human clinical trials [21], including trials in young children. Although there appear to be no age-related issues with PEP treatment in children <7 years of age [22–26], little safety data has been published in this patient group. The majority of literature on PEP usage in cystic fibrosis has focused on adolescents and adults.

EUR-1008 (Zenpep™ [pancrelipase] Eurand S.p.A., Milan, Italy) is a new, porcine-derived, enteric-coated PEP designed with a stable formulation to ensure that the product contains the label-claimed enzyme content, per the 2006 U.S. FDA guidelines for EPI drug products [21]. Two clinical trials were designed to evaluate the safety and efficacy of EUR-1008 for the treatment of EPI-associated malabsorption in patients with CF: a randomized, double-blind, placebo-controlled study in patients ≥7 years of age and a supplemental study in patients <7 years of age.

2. Materials and methods

The randomized, double-blind, placebo-controlled, two-treatment, crossover design, multicenter, phase III trial was performed at 12 U.S. sites in older patients with CF and EPI, while the supplemental, open-label, multiple-dose, multicenter, phase III study was conducted at 11 U.S. sites in younger children with CF and EPI.

2.1. Protocol development and informed consent

The Cystic Fibrosis Foundation (CFF) and the CF Therapeutics Development Network (TDN) worked with the sponsor to create both study protocols, and the protocols were approved by both the TDN and the Institutional Review Board (IRB) of each participating study site. The study designs were reviewed and approved by the CFF Data Safety Monitoring Board (DSMB) prior to implementation. Written informed consent was obtained from all adult patients (≥18 years of age) or parents/guardians of patients <18 years of age, and appropriate assent was obtained from all children per site-specific IRB policy.

2.2. Study drug and dosage

In both studies, the active study drug was provided in orally-administered capsules containing enteric-coated microspheres of porcine enzyme concentrate, which included lipase, amylase, and protease. The placebo in the randomized trial consisted of capsules filled with cellulose microcrystalline spheres, which were identical in appearance to the capsules containing active treatment.

Patients in the randomized trial could receive any of the four dosage formulations of EUR-1008 (5000, 10,000, 15,000, and 20,000 USP units of lipase/capsule), or any combination of these dosages, at the investigator's discretion during the study. The suggested starting dose for treatment in the randomized trial was 1000 lipase units/kg/meal, and the targeted maximum dose was ≤2500 lipase units/kg/meal and ≤4000 lipase units/gram fat/day. Patients in the supplemental study were administered the formulation containing 5000 USP units of lipase/capsule and were to receive approximately 2000 lipase units/kg/meal of the EUR-1008 formulation during the study. The starting dose for treatment in the supplemental study was based on the dosage of the patient's previous pancreatic enzyme therapy. The doses of EUR-1008 in both studies were given in accordance with the 1995 joint recommendations of the FDA and the U.S. Cystic Fibrosis Foundation [27], as well as the suggestion of FitzSimmons et al. [20], based on a case-control study of fibrosing colonopathy and PEP use, to limit maximum daily doses to <10,000 lipase units/kg.

In both studies, the dose was adjusted at the investigator's discretion during the dose stabilization periods based on clinical symptoms of malabsorption as reported by the patient and/or parents/guardians to determine the individual appropriate dose

that each patient was to receive during the drug treatment phase. The dose could be adjusted in steps up to 25% of the starting dose, rounded to the nearest 5000 lipase units/capsule (randomized trial) or content of a half capsule (supplemental study). Patients generally received three doses/day with their meals and a snack dose, as determined by the patient or parent/guardian. In the supplemental study, the capsules could be opened and the contents sprinkled on appropriate food whenever needed.

2.3. Patient populations and inclusion/exclusion criteria

Patients with a confirmed diagnosis of CF (sweat chloride >60 mmol/L or two CF-causing mutations) and EPI (fecal elastase of <100 μg/g stool) and age ≥7 years (randomized trial) or <7 years (supplemental study) were eligible to enroll. Patients were required to be clinically stable with no evidence of acute upper or lower respiratory tract infection, and with good nutritional status (body mass index [BMI] ≥ 20 kg/m^2 for patients age 18 years and older; BMI >25th percentile for patients age 2–17 years; or height/weight ratio >the 25th percentile for children <2 years of age [28]) and a body weight ≤70 kg. Patients were also judged by their CF physician to be candidates for a change from their existing pancreatic enzyme treatment.

Medications with the potential to affect gastric motility or stomach pH (i.e., proton pump inhibitors [PPIs], histamine-2 [H_2] blockers, motility agents, buffering agents, laxatives [including mineral oil, castor oil, and MiraLAX® (polyethylene glycol, Schering-Plough, Kenilworth, NJ)], agents for gastric ulcers, synthetic fat substitutes, fat-blocking nutritional supplements) were not permitted during either study, and patients who were unable to discontinue the use of such medications over the course of the study were excluded. Other key exclusion criteria for both studies included: history or diagnosis of fibrosing colonopathy or distal intestinal obstruction syndrome (DIOS); hyperuricemia or hyperuricosuria; hepatic insufficiency; history or current screening evaluation of hyperglycemia or CF-related diabetes; forced expiratory volume (FEV) <30% of predicted FEV_1 at Screening (randomized study only); use of an acute dose of immunosuppressive drugs within the two weeks prior to the study, oral corticosteroids, or antibiotics; history of organ transplant or bowel surgery; any respiratory condition requiring hospitalization or intensive pulmonary treatment during the study (supplemental study only); use of an enzyme preparation in excess of 10,000 lipase units/kg/day; expected inability to tolerate the washout period and/or placebo treatment (randomized study only); or allergy to pork or porcine-derived PEPs.

2.4. Study design and conduct

The study designs are shown in Figs. 1 (randomized study) and 2 (supplemental study). In both studies, after the informed consent/assent process was completed, subjects were screened at an outpatient visit. If the inclusion/exclusion criteria were met, the patients either underwent a two-day washout period from their current EPI medications (randomized study) or were changed from their existing PEP to EUR-1008 without a washout period (supplemental study) and were then titrated/stabilized on EUR 1008 before entering their respective EUR-1008 treatment period. Patients in both studies entered the dose titration/stabilization period using an enzyme dose considered by the investigator to be comparable to that used by the patient prior to study entry. The dose of EUR-1008 was then titrated by the investigator to maintain control of the clinical symptoms of EPI. The procedure for dose stabilization in the randomized study was the same regardless of whether the patient was randomized to start the first double-blind treatment period on active drug or placebo. Patients discontinued the use of any medications/foods that alter intestinal motility, gastric pH, fat absorption, or PEP activity the evening prior to entering the dose stabilization period. Patients were otherwise instructed not to change their CF care regimen components during the study, such as use of vitamin supplementation, except as stated in inclusion/exclusion criteria. During both studies, all patients were to consume a standard CF-recommended diet (45% of calories as fat, 20% as protein, and 35% as carbohydrate). A dietician reviewed the criteria for the CF diet with patients and/or their parents/guardians prior to the patient beginning the study.

In the randomized study, subjects were randomized to EUR-1008 or placebo after dose titration/stabilization using a balanced block randomization for sequence generated by an independent, unblinded statistician who was not otherwise involved in the study. Randomization assignments were obtained centrally and were not stratified by site or other factors. The order of treatments (placebo → EUR-1008 or EUR-1008 → placebo) was determined by the initial randomization scheme. After randomization, patients were treated with EUR-1008 or placebo for one week. A 72-hour stool collection, requiring a 3- to 5-day hospitalization visit during which dietary fat intake was strictly controlled, was completed over the last three days of treatment. Treatment was followed by an open-label normalization period during which patients were stabilized with EUR-1008 at the dose determined by the investigator to be optimal during the earlier dose titration/stabilization period. At the completion of this first normalization period, patients were crossed over to the alternative treatment (EUR 1008 or placebo) with a second 3- to 5-day inpatient hospitalization to complete the second 72-hour stool collection. After hospital discharge, there was a second open-label normalization period with EUR-1008, ending with a final end of study evaluation after seven days of open-label treatment were completed. Patients were on the study drug at all times except during the washout period and the blinded placebo period of the study.

During both inpatient hospitalization periods of the randomized study, a controlled diet requiring a minimum of 100 g of fat was maintained. During these periods, all food intake was recorded by the study staff at the site and reviewed by a site dietician prior to being submitted for central dietary analysis and the nursing staff dispensed all study medications to patients at meals and snacks using the predetermined optimal dose. The study staff monitored compliance with the predetermined optimal dose (determined by the investigator during dose titration/stabilization) of study

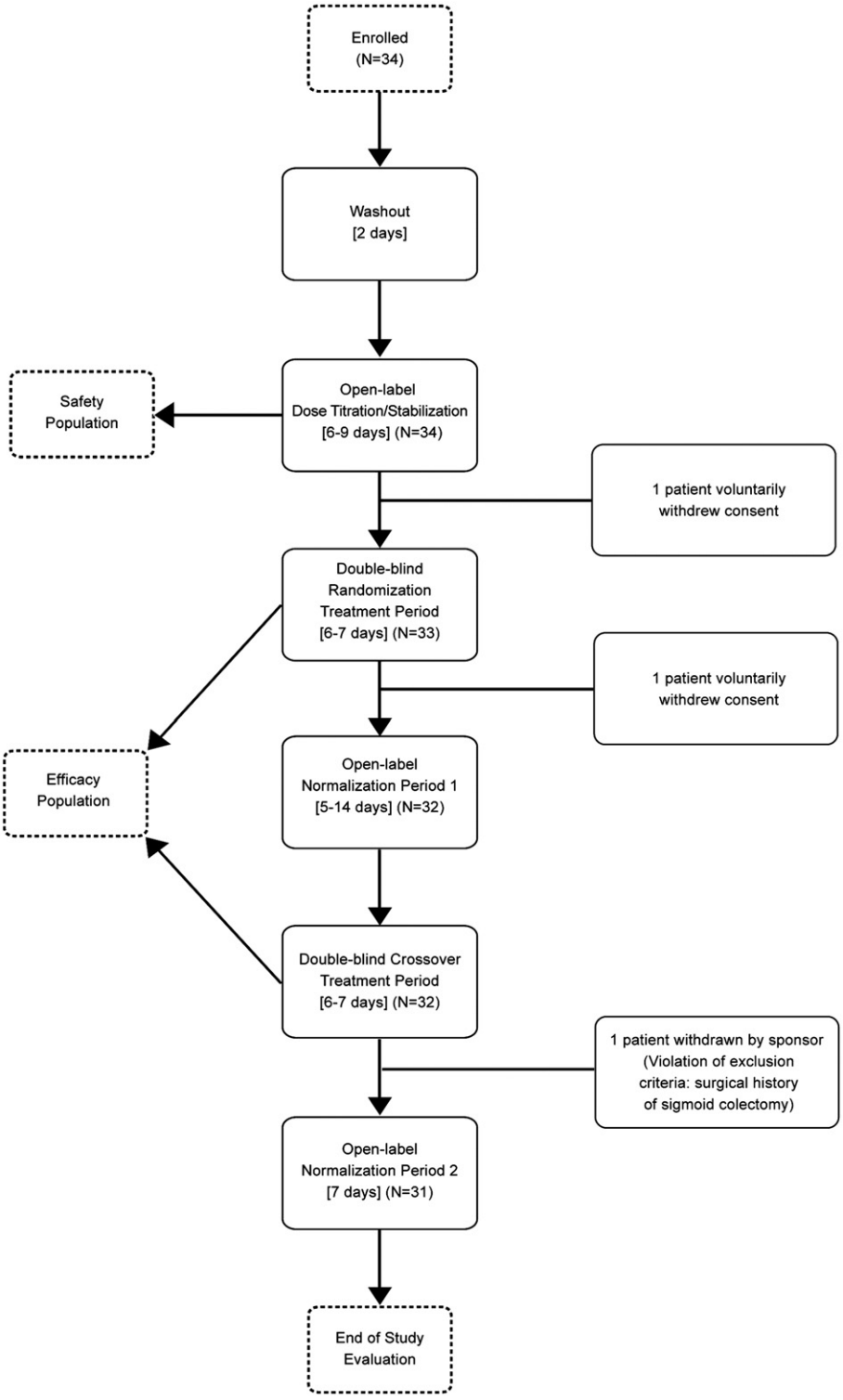

Fig. 1. Flow of the randomized study comparing EUR-1008 to placebo in patients age ≥ 7 years. The study included a washout period prior to open-label dose titration/stabilization, followed by randomized treatment, an open-label normalization period, crossover treatment, and a second open-label normalization period prior to study end.

medication for each patient during the two double-blind efficacy evaluation periods using pill counts and the dietary records maintained by patients or their parents/guardians during this time.

Prior to admission and throughout the course of the randomized study, patients or their parents/guardians maintained a diary of all food consumed, all medications taken (including each dose of EUR-1008 or placebo taken with each meal or snack), the frequency and characteristics of all stools, and signs and symptoms related to EPI malabsorption (pain, bloating, and flatulence, including severity: mild, moderate, or severe).

In the supplemental study, patients first entered a screening period of up to 14 days, during which they continued with their

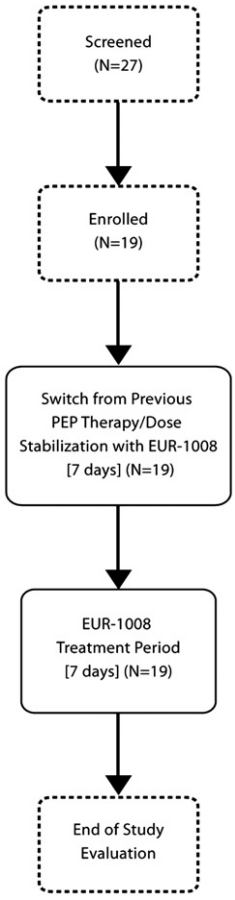

Fig. 2. Flow of the open-label, supplemental study in children age <7 years. During a screening period of up to 14 days, patients continued taking their previous pancreatic enzyme product (PEP), which they discontinued, along with any medications altering gastric pH or motility, upon entering the study. The study period consisted of a 7-day dose stabilization period using EUR-1008, followed by a 7-day treatment period with the study drug. PEP: pancreatic enzyme product.

previous pancreatic enzyme therapy. Eligible patients then entered a 7-day dose stabilization period, where they were switched from their previous pancreatic enzyme therapy (baseline) to EUR-1008 without a washout period. After the completion of the dose titration/stabilization period, subjects entered a 7-day treatment period with the study drug, with an end of study evaluation occurring on the last day of treatment.

In the supplemental study, patient adherence to the CF diet was assessed at the end of the dose stabilization and EUR-1008 treatment periods using patient dietary records (diary) kept by the parents/guardians. Parents/guardians also recorded in the diary all treatment doses, medication taken, the frequency and characteristics of stools, and symptoms such as pain, bloating, and flatulence during the study.

2.5. Evaluation of malabsorption signs and symptoms

In both studies, clinical signs and symptoms associated with EPI were assessed by the investigator/research coordinator at the study sites on the day of the study visit after the dose stabilization, normalization (randomized study only), and treatment periods by evaluating stool characteristics (frequency, consistency, presence of blood or oil/grease) and symptoms of pain, bloating, and flatulence. Stool characteristics were evaluated by the investigator/research coordinator by diary review and patient interview on the day of the study visit, and by direct observation of the stool samples collected at home and brought in for the study visit (supplemental study only).

In the supplemental study, which required that patients be without signs and symptoms of malabsorption to be considered responders, patients were considered as being without signs and symptoms of malabsorption if they had: hard, formed/normal, or soft stools; no visible blood or oil/grease in stools; no symptoms of abdominal pain; no or mild symptoms of bloating; and no or mild symptoms of flatulence. In this study, physicians and parents/guardians both evaluated patient symptoms by reviewing parent/guardian observations of malabsorption as recorded in the patient diary cards. EPI malabsorption symptoms were evaluated according to the following measures: stool frequency; stool consistency (hard, formed/normal, soft, watery, or overt diarrhea); incidences of bloating, pain, and flatulence (graded as mild, moderate, or severe); incidences of visible blood in stool; and incidences of visible oil/grease in stool. At the conclusion of the drug treatment period, physicians and parents/guardians evaluated the symptoms of EPI malabsorption as "unchanged," "improved," or "worsened" as compared to the screening period, representing the previous pancreatic enzyme therapy. Given the design of the study, where patients were switched to EUR-1008 from a previous pancreatic enzyme therapy, "no change" from the previous therapy was to be considered a positive outcome.

2.6. Stool collection and analysis

For stool collection and analysis in the randomized study, patients were administered two 250 mg brilliant blue stool markers to take with the first controlled meal of the inpatient period, and the blue markers were re-administered at the conclusion of the 72-hour controlled diet period. The first marked stool was discarded, but all subsequent stool samples were saved for analysis. At the appearance of the second stool marker, stool collections stopped, remaining evaluations were completed, and the patient was discharged.

The coefficient of fat absorption (CFA) was calculated as: [(fat intake − fat excretion) / fat intake] × 100 over the 72 h following the first appearance of blue dye in the stool. Fat intake was calculated from the dietary record by a central dietitian who input the data into The Food Processor SQL nutrition and fitness software (Version 9.6 [ESHA Research, Salem, OR]) to calculate fat excretion based on dietary intake and 72-hour fecal collection. The fat content of 72-hour stool samples was determined by nuclear magnetic resonance spectrometry [29] and the nitrogen content was determined by the Dumas combustion method.

In the supplemental study, spot fecal fat tests (acid steatocrit method) were conducted at a central laboratory at screening, at the completion of the dose stabilization period, and at the end of the 7-day treatment period using a nuclear magnetic resonance spectrometry method [29]. The stool samples for fecal fat content were collected at home (stored frozen). A value for steatorrhea of ≥ 30%

fecal fat content was utilized to represent abnormal pancreatic function as determined per a review of the literature [30–35]. The baseline steatocrit taken during screening (representing treatment with the patient's previous pancreatic enzyme therapy) was compared to the dose stabilization and treatment measurements.

3. Efficacy assessments

The primary efficacy endpoint of the randomized study was the change in the mean CFA between EUR-1008 and placebo, which was measured from the 72-hour stool sample collected during each inpatient hospitalization period. The key secondary endpoint was the change in the coefficient of nitrogen absorption (CNA) for EUR-1008 vs. placebo. Other secondary endpoints included changes in: serum cholesterol, serum vitamins A and E, body weight, BMI, and signs and symptoms of malabsorption (stool frequency and consistency; bloating, pain, flatulence).

The primary efficacy endpoint in the supplemental study was the percentage of "responders" to treatment with EUR-1008. Responders were defined as those patients without steatorrhea (<30% fecal fat content on a spot fecal fat test using the acid steatocrit) and without signs and symptoms of malabsorption after the dose stabilization and treatment periods. Patients were considered non-responders if their steatocrit was ≥30% or they showed signs and/or symptoms of malabsorption on the day of the study visit.

Secondary efficacy measures in the supplemental study included: a) nutritional status (weight change) b) physician assessment and parent/guardian observation of the control of EPI malabsorption symptoms from screening to the end of the study.

3.1. Safety assessments

Safety assessments in both studies included frequency, duration, and severity of treatment-emergent adverse events (AEs) (any event not present at baseline or any event already present that worsened in intensity or frequency from baseline), as well as clinical laboratory measurements, physical examination findings (including monitoring for DIOS), and vital sign measurement. Clinical laboratory measurements for the safety analysis included tests for uric acid in serum and urine; serum chemistry, hematology, and urinalysis; lipid profiles; and measurement of fat-soluble vitamin (A and E) levels.

Health-related quality of life (QOL) was included in the safety assessment of the randomized study only and was evaluated using the Cystic Fibrosis Questionnaire-Revised (CFQ-R) appropriate for the patient's age (<age 14 years, ≥age 14 years, and for parents/caregivers of patients <age 14 years) at screening and at the end of study visit.

All safety data was independently reviewed by the CFF DSMB.

3.2. Laboratory testing

Measurement of fecal fat, fecal nitrogen (randomized study only), serum lipids, and serum vitamin A and E levels was performed at the Mayo Clinic Department of Laboratory Medicine and Pathology (Rochester, MN). All other laboratory analyses of blood, biochemistry, and urine in the supplemental study were also performed at Mayo, while safety labs (chemistry, hematology, and urinalysis) for the randomized study were completed at the individual sites. Fecal elastase testing was performed via a monoclonal assay by Genova Diagnostics, Inc. (Asheville, NC).

3.3. Statistical methods

In the randomized study, the efficacy population (defined as all randomized patients with at least one post-baseline measurement in each treatment period) was used in the analysis of the following efficacy variables: CFA, CNA, and clinical symptoms of EPI. The primary endpoint (comparison of mean CFA between EUR-1008 and placebo) and secondary efficacy variable (CNA) were analyzed using an analysis of variance (ANOVA) model for repeated measures. A repeated measures Poisson log-linear model fitted using generalized estimating equations (GEE) was used to analyze stool frequency and symptoms of bloating, flatulence, or pain. A GEE repeated measures logistic regression model was used to analyze the binomial proportion of stools of a specific consistency, stools with macroscopically evident blood, and stools with visible oil or grease.

The safety population consisted of all patients who received at least one dose of study drug. Based on the recommendation of the CF TDN Protocol Review Committee [36] and the CFF DSMB [37], the secondary efficacy endpoints of serum total cholesterol, calculated low-density and high-density lipoprotein cholesterol (LDL-C, HDL-C), and fat-soluble vitamins were analyzed using the safety population. Treatment group comparisons of mean change from screening were performed using a paired *t*-test. As per the same recommendation, body weight and BMI were summarized using the safety population.

A *t*-test for two independent samples was used to calculate the sample size. A minimum sample of 30 (15 in each sequence) patients would have provided 90% power to detect a 23% mean difference in change in CFA at a two-sided alpha level of 0.05, assuming a common standard deviation (SD) of 27% (nQuery Advisor 4.0). A minimum sample size of 30 patients was also required to obtain sufficient safety data.

In the supplemental study, data from all patients who received at least one dose of the study drug were included in the analyses of safety and efficacy. Safety was evaluated in terms of the occurrence and severity of AEs, as well as changes in clinical laboratory parameters, physical examination findings, and vital sign measurements. No interim analyses were performed, and no analyses were required to correct for any baseline or center bias. Analyses of change from baseline to the end of study for serum vitamins A and E were done using the Wilcoxon matched pair signed rank test. When the response was highly skewed or otherwise non-symmetric, the sign test for two related samples was used.

For the primary efficacy analysis of the supplemental study, the percentage of responders between baseline and post-baseline was compared using the McNemar test and presented with 95% confidence interval and *p*-value. Change from baseline in fecal fat content was analyzed using the Wilcoxon matched pair signed

rank test. Weight change and clinical assessments of EPI were analyzed by the Wilcoxon signed rank test for continuous variables and the McNemar test for categorical variables. Change from baseline in stool frequency and number of severity-specific bloating, pain, and flatus symptoms were analyzed by fitting a repeated Poisson log-linear model using the GEE method. The proportion of stools of a specific consistency, macroscopically evident blood in stool, and visible oil/grease in stool were analyzed by fitting a repeated logistic regression model using the GEE method. Two-sided tests were used at a type I error rate of 0.05 for comparing values at baseline and 1 and 2 weeks after EUR-1008 administration. No adjustment for type I error was made for multiple comparisons.

P values in both studies were rounded to three decimal places. All analyses were conducted using SAS Version 8.2 or higher (SAS Institute Inc., Cary, NC).

4. Results

4.1. Patient characteristics

Thirty-four patients were enrolled in the randomized study at 12 study sites across the United States. All received at least one dose of the study drug and were included in the safety analyses (Safety Population). One patient voluntarily withdrew consent after dose titration/stabilization but before randomization, and one patient received EUR-1008 through the randomization treatment period and then voluntarily withdrew consent during open-label normalization period 1; these patients were excluded from the efficacy analysis. Therefore, 32 patients (mean age: 15.4 years) were considered to have completed both treatment periods and were included in the efficacy analysis (Efficacy Population).

Twenty-seven patients were screened for the supplemental study. Seven of these patients did not meet the inclusion/exclusion criteria, and one patient was lost to follow up prior to receiving the study drug. A total of 19 patients (mean age, 3.9 years) from ten sites were enrolled and completed the study.

Baseline demographic characteristics for patients in both studies are presented in Table 1.

4.2. Drug exposure and dosage

The mean exposure to EUR-1008 in the randomized trial was 29.7 days (range, 19–42 days), while mean exposure to placebo was 6.3 days (range, 4–10 days). Exposure to EUR-1008 in the open-label, supplemental study was 14 days for all patients.

During the open-label dose titration/stabilization period of the randomized study, the mean dosage (±SD) of EUR-1008 was 4591 lipase units/kg/day (±1555). The mean dosage of the study drug was similar during blinded randomization (4997 lipase units/kg/day [±1214]) and crossover treatment (5715 lipase units/kg/day [±1648]), the first open-label normalization (4469 lipase units/kg/day [±1420]), and the second open-label normalization (3887 lipase units/kg/day [±1202]). The mean drug compliance was 94.6% during treatment with EUR-1008 for both double-blind treatment periods.

In the supplemental study, the mean dosage (±SD) of EUR-1008 administered during the dose stabilization period was 5094 lipase units/kg/day (±1774), and the mean dosage during the treatment period was 5417 lipase units/kg/day (±1906).

4.3. Efficacy

In the randomized study, the estimated mean CFA and CNA for patients treated with EUR-1008 was statistically significantly higher (88.3% and 87.2%, respectively) than for patients treated with placebo (62.8% and 65.7%, respectively) ($p < 0.001$ for both endpoints) (Table 2). For CFA, the mean difference between EUR-1008 and placebo was 25.5% (95% CI: 19.3%, 31.7%), while the mean difference for CNA was 21.5% (95% CI: 16.1%, 26.9%).

Individual CFA values during placebo and EUR-1008 treatment in the randomized study are illustrated in Fig. 3. Twenty-nine patients (91%) achieved a CFA above 80% after treatment with EUR-1008, with 16 (50%) of these patients achieving a CFA

Table 1
Patient characteristics in the randomized trial (patients ≥ age 7 years) and supplemental study (patients < age 7 years).

	Randomized trial ($N=32$ [a])	Supplemental study ($N=19$)
Age (years)		
Mean (±SD)	15.4 (±4.8)	3.9 (±1.6)
Range	8–23	1–6
Age in years by category, n (%)		
≤3 years	0	9 (47.4)
4–5 years	0	7 (36.8)
6 years	0	3 (15.8)
7–13 years	7 (21.9)	0
14–17 years	12 (37.5)	0
>17 years	13 (40.6)	0
Sex, n (%)		
Male	16 (50)	12 (63.2)
Female	16 (50)	7 (36.8)
Race, n (%)		
White	30 (93.8)	19 (100)
Other	2 (6.3)	0
Height (cm)		
Mean (±SD)	154.8 (±18.1)	99.4 (±12.4)
Median	163.7	99.5
Range	114.8–176.0	76.5–121.8
Weight (kg)		
Mean (±SD)	50.4 (±14.9)	16.6 (±3.8)
Median	55.7	15.8
Range	20.3–67.4	10.1–23.4
BMI (kg/m^2)		
Mean (SD)	20.4 (3.0)	16.7 (±1.4)
Median	20.3	16.4
Range	14.8–28.2	14.4–19.5

SD: standard deviation; BMI: body mass index.
[a] Efficacy Population, consisting of all patients who completed both randomized, double-blind treatment periods.

Table 2
CFA and CNA with EUR-1008 and placebo (Efficacy Population).

	EUR-1008 (N=32)	Placebo (N=31 [a])
CFA		
LS means [b] (SEM)	88.3% (2.6)	62.8% (2.6)
p value [c]		<0.001
CNA		
LS means [b] (SEM)	87.2% (2.2)	65.7% (2.2)
p value [c]		<0.001

CFA: coefficient of fat absorption; CNA: coefficient of nitrogen absorption; SEM: standard error of the mean.

[a] One patient did not have fecal fat and nitrogen readings while on placebo.

[b] LS means (least-squares means) from an ANOVA model. LS means are estimates of means that would be expected for a balanced design.

[c] P value for testing the null hypothesis: No difference between EUR-1008 and placebo based on an ANOVA model including main effects for treatment and sequence and patient nested in sequence as a random effect.

greater than 90%. Five patients with CFA ≤ 40% during placebo treatment attained a median increase of 51% in CFA while on EUR-1008.

Compared to placebo, the clinical symptoms associated with EPI improved during treatment with EUR-1008 in the randomized study, according to information derived from patient/guardian diary reports. This included a significant reduction in stool frequency (1.8 vs. 2.7 stools/day, respectively; $p<0.001$); fewer soft (29.2% vs. 57.1%; $p<0.001$) and watery (0.4% vs. 2.6%; $p=0.013$) stools; and an increase in stool consistency that was noted as hard (16.3% vs. 6.2%; $p<0.001$) and formed/normal (53.9% vs. 33.3%; $p<0.001$). No overt diarrhea was reported while patients were taking EUR-1008.

During all treatment periods of the randomized study, the incidence of bloating, pain, and flatulence, defined as a one-hour block of time in which the patient experienced the symptom, was low. For all severities of bloating, pain, and flatulence (mild, moderate, severe), there were fewer occurrences reported while patients were receiving EUR-1008 than when receiving placebo. Macroscopically evident blood in the stool was infrequent during the study, with a mean proportion of 0.2% during blinded treatment with EUR-1008 and 1.1% during treatment with placebo. The mean proportion of stool samples with visible oil or grease was also lower during treatment with EUR-1008 as compared to placebo (6.8% vs. 28.0%; $p<0.001$), and there were statistically significant differences in favor of EUR-1008 compared to placebo in the mean incidence of moderate flatulence (0.1 vs. 0.4; $p<0.001$), mild pain (0.2 vs. 0.6; $p<0.001$), and severe pain (0.0 vs. 0.1; $p=0.007$).

The effect of EUR-1008 on reported signs and symptoms of malabsorption remained consistent throughout all four treatment periods of the randomized study (dose titration, active treatment, and both open-label normalization periods). The improvements in signs and symptoms associated with malabsorption were observed regardless of CFA values while on placebo and included improvements in patients with CFA values >80% on placebo.

Post-hoc analyses in the randomized trial's safety population for change from the screening period in total serum cholesterol, HDL-cholesterol, and serum vitamins A and E showed a statistically significant difference between EUR-1008 and placebo ($p<0.05$ for all measures) (Table 3).

Treatment order (placebo → EUR-1008 or EUR-1008 → placebo) did not appear to impact either time to normalization or response to treatment.

In the supplemental study, 11 of 19 patients (57.9%) were responders to EUR-1008 (i.e., <30% fecal fat content and without signs and symptoms of malabsorption) at the end of the drug treatment phase, compared to 10 of 19 (52.6%) at screening when they were on their previous pancreatic enzyme therapy. Of the nine patients who did not meet the criteria for "responder" at screening, six responded to EUR-1008 by the end of the study, and five of the 10 patients who were classified as responders at screening maintained their response with EUR-1008 treatment. The

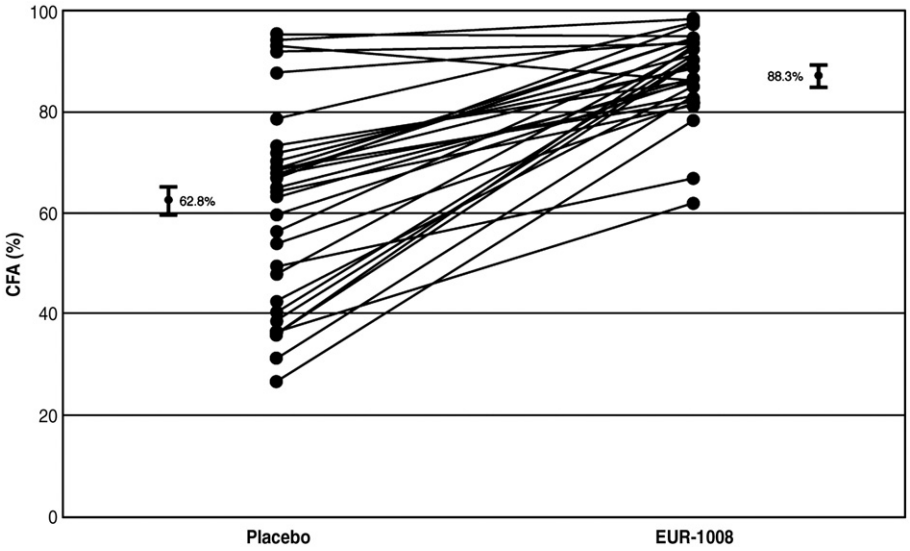

Fig. 3. Plots of the individual patient values of CFA during placebo and EUR-1008. Bars on the far left and right of figure indicate the least-squares (LS) means and the standard error (SEM) of CFA during placebo (62.8±2.6%) vs. CFA during EUR-1008 treatment (88.3±2.6%). All patients had fecal elastase (monoclonal assay) of <100 μg/g stool at screening. CFA (coefficient of fat absorption); SEM (standard error of the mean).

Table 3
Change from screening in cholesterol and vitamin levels (Safety Population).

	Screening	End of treatment	
	All patients (N=34)	EUR-1008 (N=33 [a])	Placebo (N=30 [a])
Total cholesterol (mg/dL)			
Mean (SD)	124.3 (29.5)	128.8 (30.0)	109.1 (29.8)
Mean change (SD) from screening		4.0 (21.0)	−16.1 (17.5)
p-value [b]		<0.001	
HDL (mg/dL)			
Mean (SD)	42.4 (11.0)	45.5 (10.9)	37.2 (9.2)
Mean change (SD) from screening		3.1 (8.1)	−4.8 (7.7)
p-value [b]		<0.001	
Vitamin A (mcg/L)			
Mean (SD)	380.9 (125.8)	422.3 (111.7)	363.2 (100.3)
Mean change (SD) from screening		41.6 (89.4)	−21.3 (98.6)
p-value [b]		<0.001	
Vitamin E (mg/L)			
Mean (SD)	7.4 (4.1)	8.3 (3.1)	6.7 (2.7)
Mean change (SD) from screening		0.76 (3.7)	−0.94 (3.4)
p-value [b]		<0.001	

HDL: high-density lipoprotein.
For conversion of total cholesterol and HDL mg/dL to mmol/L: multiply by 0.026.
[a] One patient receiving EUR-1008 treatment and 4 patients in the placebo treatment group failed to have a value noted in either the screening period or during at least one of the two inpatient evaluation periods.
[b] P-values were calculated to compare mean change from screening; a paired t-test was used to compare both treatment groups.

proportion of responders was not significantly different after 1 week and 2 weeks of treatment with the study drug when compared with the previous pancreatic enzyme therapy. These results are consistent with the expected result that, in young CF patients, EUR-1008 would be at least equivalent to patient's previous PEP.

Secondary endpoint analyses based on patient diaries showed that the incidences of EPI symptoms were low at all time points in the supplemental study. Most patients reported fewer than three incidences of symptoms per day, and patients experienced a significant reduction in mean stool frequency (P<0.001), incidence of moderate bloating (P=0.011), and the proportion of stool samples with visible oil or grease during treatment as compared with screening (P<0.001). All other secondary endpoints, including nutritional status, either maintained consistent with baseline measurements or showed no statistically significant changes.

None of the patients' clinical symptoms of EPI worsened during the supplemental study based on the evaluation of patient diary cards by study physicians and parents/guardians. Physicians assessed 12/19 patients (63.2%) as having no change in the control of EPI symptoms and 7/19 patients (36.8%) as having improvements in the control of EPI symptoms after treatment with EUR-1008. Parents/guardians judged 10/19 patients (52.6%) as having no change in EPI symptoms and 9/19 patients (47.4%) as having symptom improvement by the end of the treatment period.

4.4. Safety

EUR-1008 was generally safe and well-tolerated in both studies. There were no deaths during either study and no serious adverse events (SAEs) related to the study drug. In addition, no patients dropped out of either study due to an AE or laboratory abnormality.

In the randomized study, the majority of AEs for both treatment groups were mild (52%) or moderate (35%), and there were no unexpected or significant differences in the frequency or type of AEs between EUR-1008 and placebo. During the two one-week, double-blind treatment periods, approximately equal numbers of patients experienced at least one AE while receiving EUR-1008 (55.9%) compared to placebo (50.0%). The total number of treatment-emergent AEs (events not present prior to study drug exposure or those that worsened in intensity or frequency following drug exposure) was 43 for each of the double-blind treatment periods (EUR-1008 and placebo). Treatment-emergent AEs reported by the largest proportion of patients during the double-blind treatment periods were abdominal pain, steatorrhea, and headache (Table 4).

While receiving EUR-1008 or placebo, 47.1% and 37.5% of patients, respectively, reported at least one AE that was considered by the principal investigator at the study site to be possibly or probably related to study drug. The most commonly reported possibly or probably related AEs for either group were abdominal pain, flatulence, abdominal distension, abnormal feces, and steatorrhea.

Two EUR-1008 patients in the randomized study reported a serious adverse event (SAE) (hemoptysis and acute exacerbation of respiratory infection), both of which occurred during the dose titration/stabilization period. Both SAEs resolved, and both were considered by the investigators to be unrelated to the study drug.

Table 4
Treatment-emergent adverse events (≥5%) during the randomization and crossover treatment periods (Safety Population).

	EUR-1008 (N=34)	Placebo (N=32)
Total number of treatment-emergent AEs	43	43
Number of patients with ≥1 treatment-emergent AE	19 (55.9%)	16 (50.0%)
Abdominal distension	2 (5.9%)	3 (9.4%)
Abdominal pain	4 (11.8%)	6 (18.8%)
Abnormal feces	1 (2.9%)	3 (9.4%)
Flatulence	2 (5.9%)	3 (9.4%)
Frequent bowel movements	1 (2.9%)	2 (6.3%)
Steatorrhea	0	4 (12.5%)
Early satiety	2 (5.9%)	0
Contusion	2 (5.9%)	0
Weight decreased	2 (5.9%)	2 (6.3%)
Headache	5 (14.7%)	0
Cough	2 (5.9%)	0

AE=adverse event.
Adverse events were coded according to MedDRA Version 8.1.

In the supplemental study, a total of 51 treatment-emergent AEs were reported by 13 patients. Of these, 17 events (33.3%) reported by 5 patients were considered by the investigator to be possibly related to the study drug (Table 5). The most frequently reported AEs included abdominal pain, steatorrhea, feces discolored, flatulence, vomiting, abdominal discomfort, abdominal distention, and diarrhea, and were mild or moderate in severity. Two patients reported severe AEs (1 abdominal pain and 1 flatulence); both were considered possibly related to the study drug. Both events resolved in one day without treatment or discontinuation of the study drug. One patient experienced an SAE of upper respiratory tract infection that was deemed by the investigator secondary to CF and not related to study drug.

In both studies, there were no unexpected adverse trends identified in the routine safety labs of serum chemistry, hematology, and urinalysis following treatment with EUR-1008, nor were there any noteworthy changes in vital signs, physical examinations, weight, BMI, or QOL assessments as compared to baseline. In addition, no uric acid toxicity or fibrosing colonopathy was reported during either study, and there was no change in serum uric acid levels compared to placebo.

5. Discussion

The measurement of CFA on a 72-hour stool sample collected in a controlled environment is the current "gold standard" for evaluating the efficacy of enzyme replacement therapy in patients with EPI [38]. In the randomized, double-blind, placebo-controlled trial, mean fat absorption as measured by CFA was significantly higher during treatment with EUR-1008 than with placebo. Moreover, patients were more likely to achieve mean CFA levels >85%, representing "near-normal" CFA values [39], during EUR-1008 treatment as compared with placebo, and CNA was also significantly improved during treatment with the study drug as compared to placebo.

The findings of the randomized study support the known benefits of PEPs in managing malabsorption in patients with CF.

Table 5
Adverse events related to the study drug (patients <7 years of age) EUR-1008 (N=19).

	Not related (N=8)	Related (N=5)		
		Possible	Probable	Definite
Total number of AEs	34 (66.7%)	17 (33.3%)	0	0
Gastrointestinal disorders	3 (15.8%)	5 (26.3%)	0	0
Abdominal distension	0	1 (5.3%)	0	0
Abdominal pain	1 (5.3%)	4 (21.1%)	0	0
Feces discolored	1 (5.3%)	1 (5.3%)	0	0
Flatulence	0	2 (10.5%)	0	0
Steatorrhea	1 (5.3%)	2 (10.5%)	0	0
Metabolism and nutrition disorders	1 (5.3%)	1 (5.3%)	0	0
Decreased appetite	0	1 (5.3%)	0	0

AE=Adverse event.
Note: AEs are listed by system organ class preferred term. The total number of AEs includes all AEs for patients.

Mischler and colleagues reported that enteric-coated pancrelipase improved both CFA (84.1% on treatment vs. 45.7% placebo; $p<0.005$) and CNA (83.3% on treatment vs. 64.3% placebo; $p<0.01$) [40]. A study of supplemental pancreatic enzyme therapy by Konstan et al. compared two doses of pancrelipase (12,000 and 20,000 lipase units per capsule) to placebo [41]. Mean CFA and CNA was 79.4% and 83.8%, respectively, for the low-dose pancrelipase group, compared to 46.7% ($p=0.0002$) and 58.4% ($p=0.0001$), respectively, for placebo; mean CFA and CNA was 87.3% and 88.6%, respectively, for the high-dose pancrelipase group, versus 58.7% ($p=0.0001$) and 62.9% ($p=0.0001$), respectively, for placebo. In an open-label study by Stern et al. in which patients with CF and EPI received treatment for ≥6 days with delayed-release enteric-coated pancrelipase or placebo, mean CFA was 84.1% with pancrelipase treatment compared to 52.2% with placebo among patients age 7 to 18 years [42]. Finally, a prospective, randomized, controlled trial by Brady et al. found that patients receiving enteric-coated high-buffered pancrelipase had a mean CFA of 81.8% vs. 75.1% for enteric-coated-nonbuffered enzymes ($P=0.01$) [43].

The majority of patients reached normal or near-normal levels of CFA and CNA in the randomized trial while on EUR-1008 treatment, with improvement in CFA and CNA proportionately greater in patients with lower values on placebo. A similar relationship was observed in a dose-ranging study of ALTU-135, with the greatest improvements seen in subjects with baseline CFA and CNA <40% [44]. Notably, the improvements observed in the present study were achieved in the absence of any concomitant treatment affecting gastrointestinal motility or pH, suggesting that EUR-1008 alone may be as efficacious as other products that have been tested with concurrent gastrointestinal agents.

Although CFA measurement is considered the most reliable assessment of fecal fat content, it requires that the 72-hour stool collection be performed in a hospital setting, which is inconvenient and poses some risks to CF patients who are prone to infections. In addition, stool collection for measurement of CFA in young children who may still wear diapers is cumbersome and provides unreliable results, as the stool must be scraped from the diaper liner for analysis. Therefore, the primary efficacy endpoint selected for the supplemental study relied on the spot fecal fat test from a single stool sample to assess steatorrhea. This is considered a valid method for assessing fecal fat content [30–35] and was selected based upon a review of the literature and input from the investigators and the CFF-TDN.

The definition of responder used in the supplemental trial (i.e., <30% fecal fat content and without signs and symptoms of malabsorption) essentially corresponds to "normal" subjects in terms of pancreatic function, and is therefore an efficacy endpoint with a challenging threshold. Nevertheless, the results obtained at screening (when patients were on their previous pancreatic enzyme therapy) and after treatment with EUR-1008 were similar, suggesting a consistent response. Furthermore, patients had improvement in some symptoms of malabsorption after treatment with EUR-1008 (e.g., reduction of stool frequency, bloating, and stool with visible oil or grease). In addition, EUR-1008 maintained patients' control of malabsorption using doses similar to the patients' previous pancreatic enzyme therapy and did not

exacerbate clinical symptoms. Finally, EUR-1008 was perceived by physicians and parents/guardians upon review of patient diary cards to maintain or improve the control of EPI signs and symptoms vs. previous pancreatic enzyme therapies. No physician or parent/guardian assessed patients' symptoms as having worsened during the study.

In both studies, EUR-1008 was associated with clinically significant improvements in the signs and symptoms associated with EPI malabsorption in both young children and adults. Similar improvements in the signs and symptoms of malabsorption were observed by Stern and colleagues in an open-label study that demonstrated that pancrelipase mini-microspheres significantly decreased stool frequency and the incidence of soft stools [42]. Notably, the efficacy of EUR-1008 was achieved using a dose of lipase units consistent with the label claim (i.e., no enzyme overfill).

EUR-1008 was safe and well-tolerated in both studies. No patients dropped out of either study due to an AE. In the randomized trial, study drug compliance was 94.6%. The two observed SAEs in the randomized trial, hemoptysis and worsening lung disease, were assessed to be unrelated to the study drug and both resolved. There were no unexpected or significant differences in the number of AEs between EUR-1008 and placebo during the two efficacy evaluation periods, nor were there significant changes in laboratory safety values. The most commonly reported possibly or probably related AEs reported for EUR-1008 and placebo (abdominal pain, flatulence, abdominal distension, abnormal feces, and steatorrhea) are consistent with the background disease. Headache, which is reported regardless of causality, was observed during the randomized treatment period in 14.7% of patients receiving EUR-1008, but was not reported in any patients during treatment with placebo. The cause of headache while patients were on treatment is unknown; however, CF patients frequently have sinus disease and associated headache, which may help explain this finding. In the supplemental study in young patients, only two AEs possibly related to the study drug were reported as severe (1 event of abdominal pain and 1 event of flatulence), and both resolved in one day without treatment. There were no drug-related SAEs or discontinuations, nor were there any incidences of hyperuricemia or unexpected adverse trends in laboratory analyses following treatment with EUR-1008. As with previous studies of PEPs in young children [22–26], no age-related issues were noted with EUR-1008. However, these safety data may be limited by the short length of the study period (two weeks), which is too brief to detect AEs such as fibrosing colonopathy (not observed in this study).

Due to the young age of the patient population studied in the supplemental study, a number of challenges related to the choice of study controls and efficacy endpoints had to be addressed, and the design of the study was extensively discussed among the sponsor, the investigators, the CFF-TDN, and the FDA. Owing to ethical concerns about patient health and discomfort, it was considered inappropriate to remove the young children enrolled in this trial from EPI medications. Therefore, this trial did not employ a washout period or placebo control, as a lack of active treatment could lead to compromised nutritional status and considerable weight loss in this young patient population. This is significant, as weight loss during infancy or childhood correlates with poor adult pulmonary status in CF patients [5–11]. The decision to not use a placebo treatment or washout period in the design of the supplemental study is consistent with the practice reported in other published trials involving young CF patients [22–26].

In the supplemental study, EUR-1008 was effective in controlling fat malabsorption in a manner consistent with patients' previous pancreatic enzyme therapies. These results suggest that young children on PEP treatments can be rapidly and successfully switched to this new drug and obtain the benefits of a PEP formulated to meet the lipase label claim. In addition, this formulation of EUR-1008 was specifically developed for use in young children and allows the contents of the capsule to be sprinkled on foods such as applesauce and banana pudding, when necessary, allowing for convenience of administration.

In summary, EUR-1008, a new PEP for the treatment of EPI formulated to meet the label-claimed lipase enzyme content, was safe, effective and well tolerated in two clinical trials designed to meet FDA guidelines for PEPs, including demonstration of safety and efficacy endpoints that support the use of EUR-1008 for the treatment of EPI-associated malabsorption in both younger and older CF patients.

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Conflict of interest

1. Jamie Wooldridge—paid consultation agreement via salary support through Cincinnati Children's Hospital Medical Center & Scientific Advisory Board, Eurand S.p.A.
2. James E. Heubi, MD—Consultant, Scientific Advisory Board, Eurand S.p.A.
3. Samya Z. Nasr, MD—Scientific Advisory Board; Eurand S.p.A.
4. Marlyn S. Woo, MD—Scientific Advisory Board; Eurand S.p.A.
5. Cristina Straforini—Eurand S.p.A. employee
6. Marco Anelli—(50) shares of Eurand stock; Eurand employee during the planning and conduct of the trial.
7. Candace Lee, RN—Eurand, Inc., employee

The remaining authors do not have a financial relationship that creates, or may be perceived as creating, a conflict related to this article.

References

[1] Kalnins D, Durie PR, Pencharz P. Nutritional management of cystic fibrosis patients. Curr Opin Clin Nutr Metab Care 2007;10(3):348–54.
[2] Kerem BS, Buchanan JA, Durie P, et al. DNA marker haplotype association with pancreatic sufficiency in cystic fibrosis. Am J Hum Genet 1989;44:827–34.
[3] Durie PR. Pancreatic aspects of cystic fibrosis and other inherited causes of pancreatic dysfunction. Med Clin North Am 2000;84:609–20.
[4] Shepherd R, Cooksley WG, Cooke WD. Improved growth and clinical, nutritional, and respiratory changes in response to nutritional therapy in cystic fibrosis. J Pediatr 1980;97(3):351–7.
[5] Shepherd RW, Holt TL, Thomas BJ, et al. Nutritional rehabilitation in cystic fibrosis: controlled studies of effects on nutritional growth retardation, body protein turnover, and course of pulmonary disease. J Pediatr 1986;109 (5):788–94.
[6] Dodge JA. Malnutrition and age-specific nutritional management in cystic fibrosis. Neth J Med 1992;41(3–4):127–9.
[7] Thomson MA, Quirk P, Swanson CE, et al. Nutritional growth retardation is associated with defective lung growth in cystic fibrosis: a preventable determinant of progressive pulmonary dysfunction. Nutrition 1995;11 (4):350–4.
[8] Pencharz PB, Durie PR. Pathogenesis of malnutrition in cystic fibrosis, and its treatment. Clin Nutr 2000;19(6):387–94.
[9] Zemel BS, Jawad AF, FitzSimmons S, Stallings VA. Longitudinal relationship among growth, nutritional status, and pulmonary function in children with cystic fibrosis: analysis of the Cystic Fibrosis Foundation National CF Patient Registry. J Pediatr 2000 Sep;137(3):374–80.
[10] Steinkamp G, Wiedemann B. Relationship between nutritional status and lung function in cystic fibrosis: cross sectional and longitudinal analyses from the German CF quality assurance (CFQA) project. Thorax 2002;57(7):596–601.
[11] Konstan MW, Butler SM, Wohl ME, et al. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. J Pediatr 2003;142 (6):624–30.
[12] FitzSimmons SC. The changing epidemiology of cystic fibrosis. J Pediatr 1993;122(1):1–9.
[13] Cystic Fibrosis Foundation Patient Registry. Annual Data Report. Maryland: Bethesda; 2007.
[14] Whitehead AM. Study to compare the enzyme activity, acid resistance and dissolution characteristics of currently available pancreatic enzyme preparations. Pharm Weekbl Sci 1988;10(1):12–6.
[15] Kraisinger M, Hochhaus G, Stecenko A, Bowser E, Hendeles L. Clinical pharmacology of pancreatic enzymes in patients with cystic fibrosis and in vitro performance of microencapsulated formulations. J Clin Pharmacol 1994;34(2):158–66.
[16] Case CL, Henniges F, Barkin JS. Enzyme content and acid stability of enteric-coated pancreatic enzyme products in vitro. Pancreas 2005;30 (2):180–3.
[17] Borowitz D, Durie PR, Clarke LL, et al. Gastrointestinal outcomes and confounders in cystic fibrosis. J Pediatr 2005;146(2):189–93.
[18] Smyth RL, Ashby D, O'Hea U, et al. Fibrosing colonopathy in cystic fibrosis: results of a case-control study. Lancet 1995;346:1247–51.
[19] Bakowski MT, Prescott P. Patterns of use of pancreatic enzyme supplements in fibrosing colonopathy: implications for pathogenesis. Pharmacoepidemiol Drug Saf 1997;6:347–58.
[20] FitzSimmons SC, Burkhart GA, Borowitz D, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. N Engl J Med 1997;336:1283–9.
[21] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry: exocrine pancreatic insufficiency drug products—submitting NDAs. April 2006. Available at: http://www.fda.gov/cder/guidance/6275fnl.htm. Accessed June 27, 2008.
[22] Petersen W, Heilmann C, Garne S. Pancreatic enzyme supplementation as acid-resistant microspheres versus enteric-coated granules in cystic fibrosis. A double placebo controlled cross-over study. Acta Paediatr Scand 1987;76:66–9.
[23] Robinson PJ, Olinsky A, Smith AL, et al. High compared with standard dose lipase pancreatic supplement. Arch Dis Child 1989;64:143–5.
[24] Morrison G, Morrison JM, Redmond AO, et al. Comparison between a standard pancreatic supplement and a high enzyme preparation in cystic fibrosis. Aliment Pharmacol Ther 1992;6:549–55.
[25] Beker LT, Fink RJ, Shamsa FH, et al. Comparison of weight-based dosages of enteric-coated microtablet enzyme preparations in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 1994;19:191–7.
[26] Patchell CJ, Desai M, Weller PH, et al. Creon 10,000 minimicrospheres vs. Creon 8,000 microspheres—an open randomised crossover preference study. J Cyst Fibros 2002;1(4):287–91.
[27] Borowitz DS, Grand RJ, Durie PR. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, Consensus Committee. J Pediatr 1995;127:681–4.
[28] Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2002;35:246–59.
[29] Henderson AR, Rinker AD. Gastric, pancreatic, and intestinal function. In: Burtis CA, Ashwood ER, editors. Tietz textbook of clinical chemistry. 3rd ed. Philadelphia: WB Saunders; 1999. p. 1293–5.
[30] Sugai E, Srur G, Vazquez H, et al. Steatocrit: a reliable semiquantitative method for detection of steatorrhea. J Clin Gastroenterol 1994;19 (3):206–9.
[31] Tran M, Forget P, Van den Neucker A, et al. The acid steatocrit: a much improved method. J Pediatr Gastroenterol Nutr 1994;19(3):299–303.
[32] Van den Neucker AM, Kerkvliet EM, Theunissen PM, et al. Acid steatocrit: a reliable screening tool for steatorrhoea. Acta Paediatr 2001;90(8):873–5.
[33] Van den Neucker AM, Forget PP, van Kreel B. Lipid, nitrogen, water and energy content of a single stool sample in healthy children and children with cystic fibrosis. Eur J Pediatr 2003;162(11):764–6.
[34] Benini L, Caliari S, Bonfante F, et al. Fecal fat concentration in the screening of steatorrhea. Digestion 1992;53(1–2):94–100.
[35] Amann ST, Josephson SA, Toskes PP. Acid steatocrit: a simple, rapid gravimetric method to determine steatorrhea. Am J Gastroenterol 1997;92 (12):2280–4.
[36] Cystic Fibrosis Therapeutic Development Network Coordinating Center. Issue: response to the Data Safety Monitoring Board. Protocol Review Committee; December 30, 2005. p. 1–3.

[37] Cystic Fibrosis Foundation. Issue: DMC review decision. Data Safety Monitoring Board; January 06, 2006. p. 1.
[38] Borowitz D. Update on the evaluation of pancreatic exocrine status in cystic fibrosis. Curr Opin Pulm Med 2005;11(6):524–7.
[39] Littlewood JM, Wolfe SP. Control of malabsorption in cystic fibrosis. Paediatr Drugs 2000;2(3):205–22.
[40] Mischler EH, Parrell S, Farrell PM, Odell GB. Comparison of effectiveness of pancreatic enzyme preparations in cystic fibrosis. Am J Dis Child 1982;136:1060–3.
[41] Konstan MW, Stern RC, Trout JR, et al. Ultrase MT12 and Ultrase MT20 in the treatment of exocrine pancreatic insufficiency in cystic fibrosis: safety and efficacy. Aliment Pharmacol Ther 2004;20:1365–71.
[42] Stern RC, Eisenberg JD, Wagener JS, et al. A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. Am J Gastroenterol 2000;95:1932–8.
[43] Brady MS, Garson JL, Krug SK, et al. An enteric-coated high-buffered pancrelipase reduces steatorrhea in patients with cystic fibrosis: a prospective, randomized study. J Am Diet Assoc 2006;106(8):1181–6.
[44] Borowitz D, Goss CH, Limauro S, et al. Study of a novel pancreatic enzyme replacement therapy in pancreatic insufficient subjects with cystic fibrosis. J Pediatr 2006;149(5):658–62.