CLINICAL REVIEW

Application Type	NDA
Submission Number	22-210
Submission Code	N
Letter Date	December 14, 2007
Stamp Date	December 17, 2007
PDUFA Goal Date	June 17, 2008
Reviewer Name	Marjorie F. Dannis, MD
Through	Anne R. Pariser, MD
Review Completion Date	June 14, 2008
Established Name	Pancrelipase Delayed-Release Capsules
(Proposed) Trade Name	Zentase
Therapeutic Class	Pancreatic Enzyme Product (PEP)
Applicant	Eurand Pharmaceuticals Ltd.
Priority Designation	Priority
Formulation	For oral administration
Dosing Regimen	Not to exceed 2,500 USP lipase units/kg/meal or 10,000 USP lipase units/kg/day
Indication	Exocrine pancreatic insufficiency
Intended Population	Patients with exocrine pancreatic insufficiency

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This Reviewer recommends an Approvable (AE) action based upon manufacturing and product deficiencies.

From a solely clinical perspective, the safety and efficacy of EUR-1008 have been established for the treatment of patients with exocrine pancreatic insufficiency (EPI), ages one year to adult. The pivotal study EUR-1008-M demonstrated the short-term efficacy and safety of EUR-1008 for patients with Cystic Fibrosis (CF) and EPI, ages seven years to adult. The short-term safety and efficacy information obtained from Study EUR-1009-M was supportive of the treatment with EUR-1008 in pediatric patients with CF and EPI, ages one to six years. The bioavailability study, PR-001, demonstrated an acceptable short-term safety profile for treatment with EUR-1008 in patients with CF and EPI. Thus, in the opinion of this Reviewer, the clinical data submitted in the NDA are adequate to label the product for patients with EPI from one year through adulthood.

1.2 Risk Benefit Assessment

The efficacy and safety of the EUR-1008 clinical development program was demonstrated by the results of two short-tem Phase 3 trials (EUR-1008-M and EUR-1009-M). The pivotal study, EUR-1008-M, was a multicenter (US), randomized, double-blind, placebo-controlled, two-treatment, crossover study evaluating the efficacy and safety of EUR-1008 in 34 patients, ages 7 to 23 years, with a confirmed diagnosis of CF and EPI. Efficacy was assessed by the comparison of the coefficient of fat absorption (CFA) following oral administration of EUR-1008 and placebo. The results showed that there was a clinically meaningful and statistically significant increase in CFA in EUR-1008 treated patients versus patients treated with placebo. In addition, the patients who were the most severely affected (had the lowest placebo CFA level), gained the most benefit by having the largest increase in CFA.

EUR-1009-M was a multicenter, open-label, non-randomized, multiple-dose, single-treatment study evaluating the efficacy and safety of EUR-1008 in 19 patients, ages 1 to 6 years old, with confirmed diagnosis of CF and EPI. Patients who were stabilized on treatment with another pancreatic enzyme product (PEP) were enrolled in the study and switched to treatment with EUR-1008. The primary efficacy endpoint was the percentage of "responders" after one and two weeks of treatment. Responders were defined as patients without steatorrhea (<30% fecal fat content) AND without symptoms of malabsorption. The results showed that younger patients could successfully be changed from treatment with one PEP to treatment with EUR-1008 and continue to respond to therapy. This was supportive evidence of efficacy and supported the extrapolation of efficacy (and safety) to pediatric patients as young as one year of age.

Exposure to EUR-1008 (with dosages of 4,000 to 5,000 lipase units/kg/day) during both studies (EUR-1008-M and EUR-1009-M) was similar to what is currently encountered for PEP

treatment of CF patients in clinical practice. There were no deaths in either study. The few (total of 3) Serious Adverse Events (SAEs) were thought by investigators not to be related to EUR-1008 treatment. The Adverse Events (AEs) observed during the studies were consistent with the underlying diseases of the patients (mostly in the gastrointestinal and respiratory organ systems), and most were mild or moderate in severity. In general, the AE profiles reported in these studies was similar to the side-effect profiles of PEPs as reported in the medical literature.

PEPs are currently used by adult patients as well as pediatric patients as young as one month of age for the treatment of EPI due to a variety of causes. The clinical development program for EUR-1008 did not include patients less than 12 months old in any of the clinical studies; thus, the efficacy and safety have not been established for this youngest patient population. The Division is requesting that the Sponsor conduct an additional clinical trial to include patients between the ages of one month and 12 months, and the Sponsor has submitted a Deferral Request for pediatric patients under the age of one year, requesting that this study be conducted as a post-marketing commitment (PMC) once EUR-1008 is approved. At this time, the Division feels that the above Deferral Request is reasonable.

Overall, the clinical information obtained from the short-term efficacy and safety studies is adequate to support approval. With the exception of the deferred pediatric study in patients less than 12 months, no further clinical studies are required.

1.3 Recommendations for Postmarketing Risk Management Activities

No post-marketing risk-management activities are warranted at this time.

1.4 Recommendations for other Post Marketing Study Commitments

No post-marketing study commitments are warranted at this time.

2 Introduction and Regulatory Background

2.1 Product Information

EUR-1008 is the investigational agent studied in this application. EUR-1008 (pancrelipase delayed-release, Zentase, Eurand pancreatic enzyme product) is a novel, gastroprotected, porcine-derived pancreatic enzyme product (PEP) for oral administration. The active ingredient pancrelipase is a concentrated porcine extract comprised of the pancreatic enzymes lipase, amylase, and protease. EUR-1008 consists of pancrelipase formulated with either enteric-coated (EC) minitablets (dosage strengths containing 10,000, 15,000 and 20,000 USP lipase units) or EC microtablets (dosage strengths containing 5,000 USP lipase units). The EC microtablets are a special pediatric formulation that was designed to be sprinkled on food if necessary. The enteric coating is designed to facilitate the enzyme delivery into the duodenum.

The proposed trade name for this application was originally Zentase; however, this name was rejected because of its similarity to the name of another drug, Pentasa. The Sponsor has proposed two other names, Zenase and Zenpep. These new names are currently under review.

The Sponsor is proposing that EUR-1008 receive the following indication:

"EUR-1008 is indicated in patients with partial or complete exocrine pancreatic insufficiency caused by:

- Cystic fibrosis
- Chronic pancreatitis due to alcohol use or other causes
- Surgery (pancreatico-duodenectomy or Whipple's procedure, with or without Wirsung duct injection, total pancreatectomy)
- Obstruction (pancreatic and biliary duct lithiasis, pancreatic and duodenal neoplasms, ductal stenosis)
- Other pancreatic disease (hereditary, post traumatic and allograft pancreatitis, hemochromatosis Shwachman's Syndrome, lipomatosis, hyperparathyroidism)
- Poor mixing (Billroth II gastrectomy, other types of gastric bypass surgery, gastrinoma)

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The following is the Sponsor's proposed dosing regimen for meals, which follows the recommendations of the Cystic Fibrosis Foundation (CFF):

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.
- Children <4 years old eating soft or solid foods: begin with 1,000 USP lipase units/kg/meal.
- Children >4 years old: begin with 500 lipase units/kg/meal.
- Doses in excess of 2,500 USP lipase units/kg/meal should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to significantly improve a documented low coefficient of fat absorption.
- The recommended per meal dose should be halved when ingesting snacks.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with fibrosing colonopathy. Total daily dose (3 meals plus 2 or 3 snacks) should not exceed 10,000 lipase units/kg/day.[1]

The proposed age range for the use of EUR-1008 is patients aged one year through adulthood.

EUR-1008 is a New Molecular Entity (NME), and at this time there are no FDA-approved PEPs marketed in the United States (US).

[1] Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol. 2006;20(3):531-46. (PMID: 1470282)

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are many PEPs being used in the US to treat EPI in adults and children, including neonates. PEPs were first marketed in the US in the 1920's prior to the Food Drug and Cosmetic Act of 1938 (the Act). The PEPs are widely available in the US and throughout the world as nutritional supplements, and as over-the-counter (OTC) and prescription therapies; however, in the US, PEPs were never evaluated for safety and efficacy under NDA; thus, currently, there are no available PEPs marketed under an FDA-approved NDA.

2.3 Availability of Proposed Active Ingredient in the United States

EUR-1008 is not currently marketed in the US or worldwide; however, the active ingredient in EUR-1008, pancrelipase, is presently widely available from several different manufacturers as enteric coated (EC) and non-EC formulations (which are not interchangeable). Thus, many different PEP formulations are currently available in the United States and worldwide.
The availability of pancrelipase in the US is about to change secondary to the concerns about the PEPs variability in potency and safety, and the FDA is requiring that all PEPs be marketed under an approved NDA by 2010. Thus, there will no longer be PEPs available without a prescription. Please see section 2.5 for a complete description of regulatory history.

2.4 Important Safety Issues With Consideration to Related Drugs

PEPs were first marketed in the US prior to the Food Drug and Cosmetic Act of 1938; thus, they were never evaluated for safety and efficacy under an NDA. In the 1990's, concerns about variability in potency and safety (such as fibrosing colonopathy) led to a series of regulatory decisions establishing that PEPs were not generally recognized as safe and effective (GRAS and GRAE, respectively). There were substantial irregularities in potency resulting in patients being both under dosed, as well as over dosed, each presenting a different safety and efficacy concern.

The most serious safety concern with PEP administration is fibrosing colonopathy (submucosal fibrosis). Fibrosing colonopathy (FC) is a condition that has been reported mainly in young children with CF who are being administered delayed-release PEP formulations. Although the exact etiology of FC is not known, studies have shown that the majority of the patients in whom FC developed were taking high dose PEPs.[2] There was also a concern that the enteric-coating or excipients in the delayed-release PEP formulations could lead to FC. As a result of these potential efficacy and safety concerns, the CFF and FDA published weight-based dosing guidelines for PEP administration (see section 2.1). Thus, monitoring for FC should be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products, as should the CFF/FDA weight-based dosing guidelines.

[2] FitzSimmons, SC, Burkhart, GA, Borowitz, D et al. High Dose Pancreatic-Enzyme Supplements and Fibrosing Colonopathy in Cystic Fibrosis. New England Journal of Medicine. May 1997; 336 Number 18; 1283-9.

Hyperuricemia and hyperuricosuria have been reported in patients with EPI treated with PEPs. Monitoring for hyperuricemia and hyperuricosuria should be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This is the initial NDA submission for EUR-1008. Relevant pre-submission regulatory activity for EUR-1008 was notable for the following:

- During the pre-NDA meeting, there was a discussion between the Division and the Sponsor about the significance of the primary endpoint results and the Sponsor's use of the Spot Fecal Fat Test for younger patients. The Division stated that "it is not clear whether the 25% difference in CFA observed between the EUR-1008 and placebo-treated groups represents a clinically meaningful benefit to patients. The medical literature notes that in the most severely affected patients, (i.e., in patients with CFA < 40% at Baseline), an increase from baseline in CFA of 30% represents a clinically meaningful change. There is, however, no generally accepted, clinically meaningful change in CFA for less severely affected patients (i.e., patients with a Baseline CFA >40%)… We will need to review the totality of the data from this study to determine whether the results represent a clinically meaningful benefit to all patients enrolled in this study, including patients with CFA < 40% on placebo treatment and those with higher CFA during placebo treatment."

  In summary, the Sponsor was advised that achieving statistical significance of the primary endpoint may not be enough to prove efficacy of EUR-1008. The Division will need to interpret the totality of the data and make conclusions on efficacy after examining all the relevant information to determine if the results of their studies are clinically relevant.

- There was an agreement established between the Sponsor and the Division regarding the use of the Spot Fecal Fat Test as opposed to the 72-hour stool collection. The Sponsor was responsible for fulfilling the following requirements:

    - Submit the source articles that support the use of spot fecal analysis.

    - Obtain simultaneous measurements of the average of three acid steatocrits and 72-hour collections during EUR-1008-M to assist in validating the nuclear magnetic resonance (NMR) spectroscopic measurement for use in younger children.

    - Use the means of three random samples obtained on different days instead of a single sample to minimize variations in single samples created by inconsistent dietary intake.

    - Address the issue of providing a consistent dietary intake (e.g., 100-150 g fat/day) for three days prior to and during each sample collection.

- Specify the number of samples required in a child producing more than 1 stool per day.

- Specify the efforts made to minimize contamination of the stool collection by urine in the protocol.

However, the sponsor stated that the study had been completed, and they could not retrospectively go back and redo these collections. Thus, the Division agreed to review the data as collected in the study, and to consider the results as a review issue, although limitations were noted in the testing method, and that this testing method would be considered only for this limited patient population.

The regulatory background of the PEPs is as follows:

PEPs were first marketed in the US in the 1920's prior to the Food Drug and Cosmetic Act of 1938 (the Act). The PEPs are widely available in the US and throughout the world as nutritional supplements, and as OTC and prescription therapies; however, PEPs were never evaluated for safety and efficacy under an NDA.

Due to concerns about variability in potency, the Agency published a Notice of Proposed Rule making in the Federal Register (FR) on 15-July-1991 establishing that PEPs are not considered GRAS and GRAE, and the PEPs were considered misbranded. Concurrently, the Agency declared its intention to consider all PEPs to be new drugs requiring an approved NDA for continued marketing. This position was reaffirmed on 25-April-1995 with the publication of a Final Rule calling for all PEPs to be marketed drug products under approved NDAs in order to remain on the market. In April 2004, the Agency published in the FR a Notice of Requirement for NDA Approval of all PEPs within the next four years, with a deadline of 28-April-2008. In October 2007, enforcement discretion was extended until April 2010, but all PEPs must have an open IND by 28-April-2008.

In April 2006, The Guidance for Industry; Exocrine Pancreatic Insufficiency Drug Products was published[3] (the Guidance). In this document, the FDA stated its expectation that animal-(porcine- and bovine-) derived PEP NDA applications would be submitted as 505(b)(2) applications. In these submissions, Sponsors were allowed to have a limited clinical development program, which could include short-term studies to establish efficacy and safety. These abbreviated clinical development programs are acceptable for PEP applications because assumptions were made about the efficacy and safety of these drugs based on a large body of efficacy and safety information available in the medical literature. The PEPs are also considered to be the standard of care for EPI due to CF and other causes, as described in the current CFF consensus statement.

[3] U.S. Department of Health and Human Services. Food and Drug Administration .Center for Drug Evaluation and Research (CDER). "Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products –Submitting NDAs." (http://www fda.gov/Cder/guidance/6275fnl.pdf). April 2006.

2.6 Other Relevant Background Information

Pancreatic Enzyme Products (PEPs) are currently used by adult patients as well as pediatric patients as young as one month of age for the treatment of EPI due to a variety of causes. The clinical development program for EUR-1008 did not include patients less than 12 months old in any of the clinical studies; thus, the efficacy and safety have not been established for this youngest patient population. The Division is requesting that the Sponsor conduct an additional clinical trial to include patients between the ages of one month and 12 months, and the Sponsor has submitted a Deferral Request for pediatric patients under the age of one year, requesting that this study be conducted as a post-marketing commitment (PMC) once EUR-1008 is approved. At this time, the Division feels that the above Deferral Request is reasonable.

The Sponsor's proposed trial design for the pediatric study in patients less than one year of age is

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The Division will continue the negotiations with the Sponsor about the performance of this study as a post-marketing study commitment, should EUR-1008 be approved in a subsequent review cycle.

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the clinical information contained in this submission was acceptable.

3.2 Compliance with Good Clinical Practices

The Sponsor states that study EUR-1008-M and study EUR-1009-M were carried out in accordance with Good Clinical Practice (GCP) guidelines.

DSI inspections of selected clinical sites were performed, and included the inspection of Site 105 (Dr. Steven Boas, Glenview, IL) and Site 103 (Dr. David Schaeffer, Jacksonville, FL). These sites were selected by the Division based on number of patients enrolled, and the number of treatment responders at these sites. The central laboratory ((b) (4)) was also audited, with the audit limited to confirmation of the primary endpoint results, since all of the laboratory evaluations of the primary endpoint for the pivotal study were performed at this laboratory. The recommendation by DSI Investigator Khairy Malek, M.D. is that "the data are reliable and can be used in support of the NDA."

3.3 Financial Disclosures

Financial disclosure forms were reviewed and all but one Investigator who participated in the three clinical studies reported no financial interests. Dr. (b) (6), who was a clinical investigator for (b) (6), received the following payments from Eurand:

- Two unrestricted grants of $78,780 and $15,000
- Honoraria of $2,000

In the opinion of this Reviewer, (b) (6) thus, any financial interests of the investigator would not affect the overall study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CMC data have been extensively reviewed by the Drug Product and Drug Substance Reviewer, Howard Anderson, Ph.D. His recommendations are for an approvable action based on multiple drug product and multiple drug substance deficiencies. Please see these reviews for more detailed information.

4.2 Clinical Microbiology

According to Microbiology Reviewer, Stephen E. Langille, Ph.D., the drug product is a solid oral dosage form with microbial limit specifications and no microbiology deficiencies identified. Thus, NDA 22-210 was recommended for approval on the basis of a satisfactory product quality microbiology review. Please see the Microbiology Review for more detailed information on the microbiology data.

4.3 Preclinical Pharmacology/Toxicology

Since extensive human experience exists with the PEPs, and consistent with recommendations in the Guidance, no non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA. Please see the Nonclinical Pharmacology Review (by Ke Zhang, Ph.D.) for more detailed information on the nonclinical information relevant to this NDA submission.

4.4 Clinical Pharmacology

Clinical Pharmacology data have been extensively reviewed by the Office of Clinical Pharmacology (OCP) and "OCP is of the opinion that the clinical pharmacology section of this NDA is not acceptable." Please see the Clinical Pharmacology Review (by Tien-Mien Chen, Ph.D.) for more detailed information on the clinical pharmacology data. Important findings from Dr. Chen's review are as follows.

The NDA is not acceptable from a Clinical Pharmacology standpoint for the following reasons:

1. Regarding the in vivo intubation bioavailability study (PR-001):

a. The quantity of lipase recovered in one patient following administration of food only was approximately 35,000 units which was substantially greater than that (zero units) following administration of Zentase (EUR-1008) with food. Even if the drug was not released in this patient due to the low pH in the duodenum, this does not explain "zero" lipase recovery when Zentase was given with food. This raises a question on the reliability of the overall study results.

b. It is not clear how the methodology ensures that the lipase recovered from the duodenum aspirations represents the total lipase available in the duodenum. This information was requested but the sponsor has not responded to this request.

c. The number of patients is too small (N=8) in view of the high variability observed in the study.

2. Regarding the *in vitro* stability data (from Study PR-001):

a. For three batches of Zentase (EUR-1008) capsules provided in this NDA, the individual data for two of the three batches were identical. It is not clear if there were errors in the dataset. An information request for clarification was made but the sponsor has not responded to this request.

b. Some patients had very high endogenous lipase levels at baseline and under fed conditions (giving food only). It would appear to be a better approach to select and enroll only the patients with significant pancreatic enzyme insufficiency and to have an assay method specific to the exogenous pancreatic lipase as well.

Please see Clinical Pharmacology Review for complete details.

4.4.1 Mechanism of Action

EUR-1008 acts locally in the gastrointestinal (GI) tract to improve the absorption of lipids, fat soluble vitamins, proteins, and to a lesser extent carbohydrates; it is not systemically absorbed.

4.4.2 Pharmacodynamics

Lipase, amylase, and protease act locally in the GI tract and are not systemically absorbed; therefore, pharmacodynamic studies are not applicable.

4.4.3 Pharmacokinetics

PEPs act locally in the GI tract and are not absorbed; therefore, pharmacokinetic studies are not applicable.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

There were three clinical studies conducted in the EUR-1008 clinical development program; the pivotal study, EUR-1008-M, the supportive study, EUR-1009-M, and the bioavailability (BA) study, PR-001. See Table 1 for a listing and summary of these studies.

Table 1: Clinical Studies for EUR-1008

	Study	Study ID	Number of Sites	Number of Patients Enrolled	Design	Primary Endpoint
Studies in Support of Efficacy	*Pivotal Study*	EUR-1008-M	12	34	Randomized, multicenter, double-blind, placebo-controlled, 2-treatment, crossover study	To compare the CFA during oral administration of EUR-1008 or placebo in CF patients with EPI, ages seven to adult
	Supportive Study	EUR-1009-M	10	19	Multicenter, non-randomized, open-label, multiple-dose, single-treatment study	To compare the responder rate and fecal fat excretion in CF patients with EPI before (while on prior PEP) and after administration of EUR-1008 in CF patients with EPI, ages one to six years
Other Studies	*Bioavailability Study*	PR-001	1	11	Randomized, open-label, single-treatment, crossover study	To determine the gastrointestinal bioavailability of EUR-1008 in chronic pancreatitis (CP) patients with EPI

5.2 Review Strategy

The two new Phase 3 clinical studies submitted to this application are reviewed in detail; these are the pivotal study, EUR-1008-M, and the supportive study, EUR-1009-M. Review of the bioavailability study, PR-001, was deferred to Clinical Pharmacology; however, adverse event data were included in the safety analysis.

The majority of time was spent reviewing the pivotal study, EUR-1008-M; efficacy of EUR-1008 was established from this randomized, double-blind, placebo-controlled study. EUR-1009-M, an open label, non-randomized trial was used as supportive evidence of efficacy and supported the extrapolation of efficacy (and safety) to pediatric patients as young as one year of age.

This NDA was submitted as a 505(b)(2) application. To obtain approval, PEP NDAs must meet the requirements for clinical studies described in 21 CFR 314.50. The Agency determined that

there was a considerable body of evidence that replacement of pancreatic enzymes has clinical benefit for patients with cystic fibrosis and chronic pancreatitis (69 FR 23410). Thus, the limited clinical development program of EUR-1008 (one small pivotal study, one small supportive study) was acceptable.

5.3 Discussion of Individual Studies

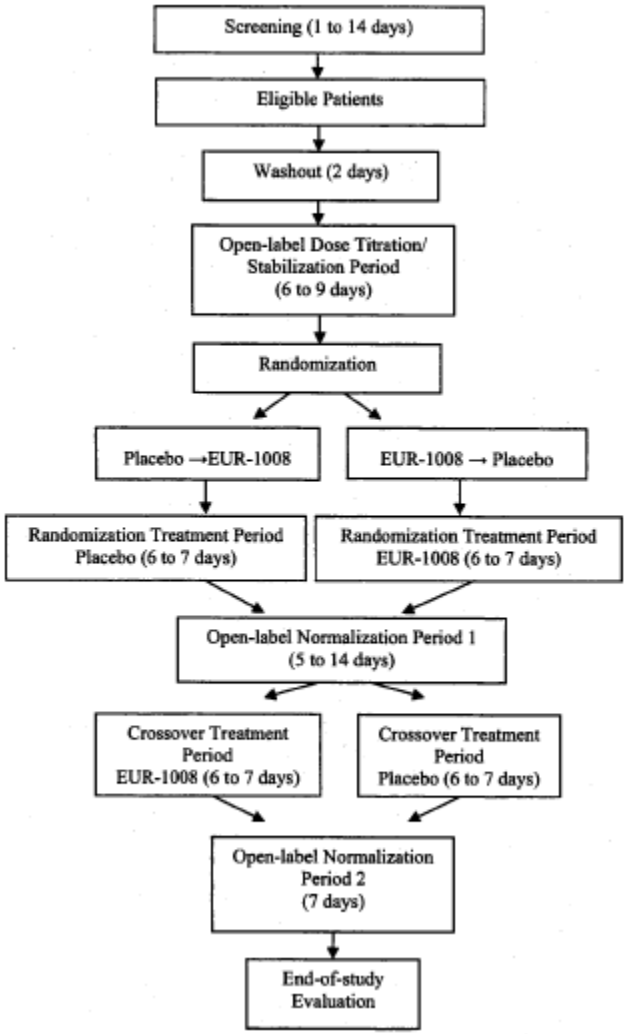
5.3.1 EUR-1008-M

5.3.1.1 Study Design

The pivotal study, EUR-1008-M was a multicenter (US), randomized, double-blind, placebo-controlled, two-treatment, crossover study evaluating the efficacy and safety of EUR-1008 in 34 patients, ages 7 to 23 years, with a confirmed diagnosis of Cystic Fibrosis (CF) and Exocrine Pancreatic Insufficiency (EPI). Efficacy was assessed by the comparison of the coefficient of fat absorption (CFA) following oral administration of EUR-1008 and placebo. The study was conducted between May 15, 2006 and November 28, 2006.

The study design consisted of: a washout period (2 days, no PEPs) an open-label dose titration/stabilization period (6 to 9 days of varying EUR-1008 doses), a randomization treatment period (6 to 7 days), an open-label normalization period (5 to 14 days of stable EUR-1008 dose), a cross-over treatment period (6 to 7 days), and a second open-label normalization period (7 days of stable EUR-1008 dose). The overall study design is represented graphically in Figure 1 (electronically copied and reproduced from the Sponsor's submission).

Figure 1: Overall Study Design



5.3.1.2 Study Objectives

The objectives of the study were to evaluate the short-term safety and effectiveness (by a 72-hour fecal fat collection) of EUR-1008 as compared to placebo in patients with EPI due to CF.

5.3.1.3 Patient Population

5.3.1.3.1 Key Inclusion Criteria

Patients were eligible for study participation if they were males or females seven years of age and older, and:

- Had confirmed diagnoses of CF - Two clinical features consistent with CF *and* genotype consistent with CF or sweat chloride concentration > 60 mEq/L, and

- Had confirmed diagnosis of EPI - Currently receiving treatment with another PEP (EUR-1008 is not currently marketed in the United States) and documented fecal elastase < 100 micrograms/g stool.

5.3.1.3.2 Key Exclusion Criteria:

Patients were excluded from study participation if they had any of the following exclusion criteria:

- History of fibrosing colonopathy.
- Had recent illness involving acute systemic administration of antibiotics within previous four weeks or acute steroid use within previous two weeks.
- History of solid organ transplant or major bowel surgery.
- Use of immunosuppressive drugs.
- Use of enzyme preparation greater than 10,000 lipase units per kg/day.

5.3.1.4 Concomitant Medications

Concomitant administration of the following classes of medications was prohibited during the study: proton pump inhibitors (PPI), histamine (H2) receptor blockers, and other agents that alter gastric pH, motility agents, buffering agents, laxatives, synthetic fat substitutes, and fat-blocking agents. All other medications were permitted for use during the study, and were recorded on the case report forms (CRFs).

5.3.1.5 Study Visits and Procedures

The majority of study visits were in the outpatient setting (study Visits 1, 2, 3, 4, 6, 7, and end-of-study). During Visits 5 and 8, patients were hospitalized for three to five days wherein they were fed a controlled diet and underwent testing every day. The two, 72-hour stool collections were performed during the inpatient stays for Visits 5 and 8. The study visits and procedures are summarized in Table 2 (electronically copied and reproduced from the Sponsor's submission).

Table 2: Schedule of Study Assessments

	Screening	Wash-out	Dose Titration/ Stabilization Period (Open-label)		Randomization Treatment Period		Normalization Period 1 (Open-label)	Crossover Treatment Period		Normalization Period 2 (Open-label)
Total Days Needed	Up to 14 days	2 days	6 to 9 days		6 to 7 days[n]		5 to 14 days	6 to 7 days[n]		7 days
Study Day			Day 1[a]	Day 6[b]	Day 1	Days 3, 4, 5, 6	Day 6[c]	Day 1	Days 3, 4, 5, 6	Day 7
	Visit 1	**None**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**End-of-study**
Informed consent	X									
Medical history	X									
Complete physical examination[d]	X									X
Abbreviated physical examination[e]			X	X	X	Daily	X	X	Daily	
Abdominal x-ray for DIOS	X									
Assessment of DIOS			X	X	X	Daily	X	X	Daily	X
Spirometry	X									
CF quality-of-life questionnaire[f]	X									X
Serum pregnancy test[g]	X									X
Fecal elastase[h]	X									
Clinical chemistry[i], hematology, urinalysis[k]	X[j]					Day 6[r]			Day 6[r]	X
Study drug provided[p]			X		X	Daily		X	Daily	
Hospital diet record[l]						Daily			Daily	
Clinical symptoms of EPI[m]			X	X	X	Daily	X	X	Daily	X
Stool collection for fecal fat and nitrogen (72-hour stool sample)						Daily			Daily	
AEs and concomitant medications		X	X	X	X	Daily	X	X	Daily	X
Maintenance/review of diary[o]	X	X	X	X	X	Daily	X	X	Daily	X
Dye administration[q]						X			X	

AE = adverse event, CF = cystic fibrosis, DIOS = distal ileal obstruction syndrome, EPI = exocrine pancreatic insufficiency, PIVKA II = des-carboxylated prothrombin protein induced by absence of vitamin K

[a] All time points are ± 1 day

[b] Same assessments to be done on Study Visit 3b (Day 9 ± 1 day), if such visit is needed

[c] Same assessments to be done on Study Visits 6b (Day 9 ± 1 day) and 6c (Day 14 ± 1 day), if such visits are needed

[d] Assessment of body systems, height, weight, vital signs

[e] Abdominal examination, weight, and vital signs only

[f] See Appendix B of the Protocol.

[g] For women of childbearing potential

[h] For determination of fecal elastase if no documentation of fecal elastase available

[i] Including serum uric acid, total cholesterol, HDL-C, calculated LDL-C, and vitamins A, E, and PIVKA II

[j] Fasting blood glucose at Screening; non-fasting at other time points

[k] Including urinary uric acid

[l] Diet recorded by study dietician on Days 3, 4, and 5 of both in-hospital treatment periods

[m] Stool frequency, stool consistency, bloating, flatulence, pain, macroscopic blood in stool, and appearance of oil or grease in the stool

[n] The excretion of the dye in the stool may require an additional 24-36 hours, which increases the patients' stay in the hospital to Day 7

[o] Diary included home diet record, home study drug use record, medication use, clinical symptoms of EPI, and adverse events

[p] EUR-1008 during open-label dose titration/stabilization and open-label periods; EUR-1008 or placebo during randomization and crossover treatment periods

[q] Dye is administered on Days 3 and 6 for the 72-hour stool sample

[r] Fasted blood samples were drawn on the morning of Day 6 regardless of the appearance of any dye marker in the stool

5.3.1.6 Randomization and Controls

A balanced block randomization for sequence was generated by an unblinded statistician not involved in the study; randomization assignments were obtained centrally and were not stratified by any factor. The order of treatments was determined by randomization at the beginning of the randomization period, and continued through the crossover period. Patients were assigned to either sequence 1 (EUR-1008 then placebo) or sequence 2 (placebo then EUR-1008).

The study drugs were packaged in sealed bottles each containing 100 capsules. The placebo capsules were identical in appearance to the active treatment capsules. Throughout the trial, each patient received treatment packs containing the maximum allowable dose of 10,000 lipase units/kg/day or 4,000 lipase units/g fat/day for each treatment phase.

A central laboratory determined fecal elastase at study entry, and fecal fat content and fecal nitrogen content during the treatment period of the study.

5.3.1.7 Study Medication Dose Selection, Dispensing, and Compliance

The starting dose of EUR-1008 treatment was at a dose considered by the investigator to be comparable to the dose (by lipase units) used with the pre-study PEP. This dose was titrated by the investigator to control clinical symptoms of EPI (as reported by the patient), yet could not exceed 2,500 lipase units/kg/meal and 4,000 lipase units/gram fat/day. The dose was titrated by increases up to 25% of the starting dose, rounded to the nearest 5,000 lipase units/capsule (to avoid unblinding by opening the capsule). The total dose was not to exceed 10,000 lipase units/kg/day. Doses were obtained using combinations of all four unit strengths of EUR-1008 intended for commercialization.

Due to the study design of this study, the mean days of exposure to EUR-1008 was considerably longer than the mean days of exposure to placebo, 30 vs. 6, respectively.

Patients received one sealed package of study medication at the beginning of each study period; the package was identified with the unique patient study number and contained the study drug for that study period. According to the Sponsor, the packaging of the study drug was performed by a certified packager in accordance with ICH E6 (R1).

Study staff monitored compliance with the predetermined doses of study medication during each of the two efficacy evaluation periods (Study Visits 5 and 8). Patients were instructed to record each dose of EUR-1008 taken with each meal or snack to determine the total daily dose. The investigator maintained records of receipt of all study medication including when and what doses were used by each patient. Patient compliance was determined based on the percentage of treatment compliance (whether the predetermined optimal dose of study medication was taken).

5.3.1.8 Efficacy and Endpoint Measures

5.3.1.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the comparison of the coefficient of fat absorption (CFA) after administration of EUR-1008 versus placebo. CFA was determined from the fat intake (calculated from the 72-hour dietary records) and fat excretion (from the 72-hour stool collection) during the efficacy evaluation period (Days 3, 4 and 5) of each double-blind treatment period. Food intake was strictly controlled and recorded for 72 hours by qualified site personnel. The fecal fat measurements were obtained during a 72-hour in hospital stool collection. CFA was calculated as:

$$\frac{\textit{fat intake} - \textit{fat excretion}}{\textit{fat intake}} \times 100$$

The efficacy analysis population was defined as all patients who received treatment and completed at least one post-baseline measurement for each period of the treatment sequences.

5.3.1.8.2 Secondary Endpoints

Secondary endpoints included the comparison of and changes in (EUR-1008 vs. placebo):

1. The coefficient of nitrogen absorption (CNA),
2. Blood levels of total cholesterol, calculated LDL-C, HDL-C, fat-soluble vitamins (A,E) and protein induced by vitamin K absence (PIVKA II),
3. Weight loss/gain and BMI, and
4. The incidence of clinical symptoms of EPI (stool frequency and consistency; intestinal bloating, pain and flatulence). Quality of life (Qol) was also evaluated at the beginning and at the end of the trial by Qol questionnaires.

5.3.1.8.3 Safety Endpoints

Safety endpoints included assessments of or changes in frequency, duration, and severity of treatment-emergent AEs, clinical laboratory parameters, physical examination findings, and vital sign measurements in the safety population. The safety analysis population was defined as all patients who received at least one dose of study drug (N=34).

5.3.1.9 Statistical Considerations

The primary endpoint comparison of CFA observed during treatment with placebo and during treatment with EUR-1008 was done using an analysis of variance appropriate for the crossover design. A *t* test for two independent samples was used to calculate power and sample size. An estimate of within-patient variance for calculating the effect size was not available; thus, the between-patient pooled variance was used instead.

A minimum sample of 30 (15 in each sequence) provided 90% power to detect a 23% mean difference in change in CFA (at a two-sided alpha level of 0.05 and standard deviation of 27%).

5.3.1.10 Protocol Amendments

There were two amendments to the original protocol, dated October 17, 2005. Potentially significant changes to the protocol included in these amendments were:

- The screening period was extended from one to four days to one to 14 days. According to the Sponsor, this change was secondary to a prolonged turn around time of the central laboratory's fecal elastase determinations.
- An interim analysis was added to the protocol (formerly there was none) and will be performed when 50% of the patients have completed the treatment. According to the Sponsor, this analysis will not include efficacy, but will be limited to:
    - Number of patients screened, enrolled, and randomized.
    - Reasons for failure to complete the trial.
    - Protocol deviations and violations.
    - AEs and Serious Adverse Events (SAEs).

Changes in the Planned Analysis:
There were minor changes made in the Statistical Analysis Plan (SAP) after the lock of the clinical database. According to the FDA Statistician, Freda Cooner, Ph.D., these changes did not have an effect on the overall results of the study.

5.3.1.11 Study Results

5.3.1.11.1 Demographics

There were 34 patients between the ages of 7 and 23 years enrolled in EUR-1008-M. There was equal representation of males and females. Less than 24 percent of these patients were between the ages of 7 and 11 years, almost 35 percent were 17 years of age or older, and approximately 41 percent were between the ages of 12 and 16 years. The patients were mostly homogeneous in terms of race and ethnicity with the majority of patients being non-Hispanic and Caucasian. Since CF is a disease predominantly of Caucasians, the study population is representative of the CF population. The demographics of patients enrolled in Study EUR-1008-M are summarized in Table 3.

Table 3: Demographics of EUR-1008-M

Demographic Variable	**N=34**	
Age (years)	Mean (SD): Range:	15.5 (4.6) 7-23
Age categories	7-11: 12-16: ≥17:	8 (24%) 14 (41%) 12 (35%)
Gender	Male: Female:	17 (50%) 17 (50%)
Ethnicity	Hispanic: Non-Hispanic:	3 (9%) 31 (91%)
Race	Caucasian: Non-Caucasian:	32 (94%) 2 (6%)
Duration (yrs) of CF diagnosis	Mean (SD): Range:	14 (5.5) 3-23

5.3.1.11.2 Patient Disposition

Thirty-four patients were enrolled in Study 1008-M, 33 patients were randomized, and 31 patients completed the study. Information about Screen failures was not available. There were 12 study sites with between one and six patients enrolled at each site. Enrollment by site is summarized in Table 4.

Table 4: Patients per Study Site

Site Number	**101**	**102**	**103**	**105**	**106**	**108**	**109**	**112**	**115**	**116**	**117**	**118**
	101802	102802	103801	105801	106801	108801	109803	112801	115801	116801	117802	118802
	101804		103802	105803		108802	109804	112803	115802	116802	117801	118803
	101805		103803	105804			109805	112804	115803			
			103804	105805			109806	112805				
				105806								
				105807								
Total Patients	**3**	**1**	**4**	**6**	**1**	**2**	**4**	**4**	**3**	**2**	**2**	**2**

There were two patients who voluntarily withdrew consent, one patient before randomization (117802) and one patient after (117801). The Sponsor withdrew one patient (108802) prior to study completion secondary to discovering that the patient had undergone a sigmoid colectomy (protocol violation). This patient had a Baseline CFA of 95. There were no patients who experienced adverse events that caused them to discontinue from the study. Patient disposition is summarized in Table 5.

Table 5: Study 1008-M Patient Disposition

Population	**Number of Patients**
Enrolled	N=34
Randomized	N=33
Completed DB treatment	N=32
Completed study	N=31
Voluntarily withdrew consent	N=2 (one pt. before randomization; one pt. after)
Sponsor withdrew patient	N=1 (had sigmoid colectomy)
AEs causing discontinuation	N=0

5.3.1.11.3 Concomitant Medications

The most commonly reported concomitant medications during the EUR-1008 treatment period and the placebo treatment period were multivitamins (MVIs) (79% and 78%, respectively), dornase alfa (74% and 78%, respectively), salbuterol (74% and 72%, respectively), and tobramycin (56% for both). There were 18/32 (56%) of the efficacy population who were taking PPIs, H2 blockers or antacids prior to study enrollment; these medications were discontinued after these patients were enrolled in the study.

It is likely that many patients with CF use the medications mentioned above; thus, the medications taken by the study population would be representative of the medications that will be used by the intended population post approval.

5.3.1.11.4 Compliance with Study Medication

Patient compliance with the study drug was determined in each of the two efficacy evaluation periods (Study Visit 5 and Study Visit 8) based on the percentage of treatment compliance (whether the predetermined optimal dose of study medication was taken). According to the Sponsor, the original algorithm to determine this value was changed after review of the initial data. Percent of treatment compliance was based on the dosage per kg of body weight for the first full day in the hospital for each study period (Study Visit 5: Day 4, and Study Visit 8: Day 4). Treatment compliance was similar for both double-blind treatment periods during treatment with EUR-1008 as well as treatment with placebo, and compliance was high in both treatment groups. The mean study drug compliance during treatment with EUR-1008 was 95% of the prescribed dose and during treatment with placebo was 100% for both double-blind periods.

5.3.1.11.5 Dosing Information/Exposure

During the open-label titration/stabilization period and the open label normalization period 1, the mean dosage of study drug was approximately 4,500 lipase units/kg/day. Dosages were slightly higher during the randomized treatment period and crossover treatment period with a mean dose of 5,366 lipase units/kg/day for patients receiving EUR-1008 and 5,517 lipase units/kg/day for patients receiving placebo. The mean dosage was slightly lower during the open-label normalization period 2 at 3,887 lipase units/kg/day. Patients in this study were exposed to EUR-1008 for a longer period of time than the exposure to placebo (29.7 days vs. 6.3 days).

5.3.1.11.6 Protocol Deviations and Violations

A total of 135 protocol deviations and 30 violations occurred during this study. Many of the deviations and violations were minor and related to study visit timing and laboratory assessments. Most of the patients with deviations/violations were included in the efficacy analysis population. Of note is the inclusion of a protocol violator in the efficacy analysis (patient who had a colectomy). This patient had a high placebo CFA (95%), thus including this patent in the efficacy analysis would have lowered the mean change in CFA. However, since there still was a statistically significant result of the primary endpoint with inclusion of this patient, the primary efficacy analysis was not significantly affected. None of the deviations/violations represented a significant safety concern for EUR-1008. Please see Statistical Review by Freda Cooner, Ph.D. for further details.

5.3.1.11.7 Efficacy Results

5.3.1.11.7.1 Primary Efficacy Analysis

The primary endpoint in Study 1008-M was the change in the CFA in the efficacy population. The CFA measured during treatment with EUR-1008 was compared with the CFA measured during treatment with placebo. Thirty-two patients who completed both double-blind treatment periods were included in the efficacy analysis population.

The Sponsor's results show that the mean CFA for patients receiving EUR-1008 was 88% (SD= 7.9); the mean CFA for patients receiving placebo (no treatment) was 63% (SD=19.1). Therefore, the mean change in CFA was 25%. The efficacy results show a mean change in CFA that was statistically significant ($p < 0.001$; 95% CI [-31.7, -19.3]). The FDA Statistician confirmed the results and was agreement with the Sponsor. The results are summarized in Table 6 (electronically copied and reproduced from the Sponsor's submission).

Table 6: ANOVA Model Results of Coefficient of Fat Absorption (CFA, %)

	EUR-1008 (N=32)	Placebo (N=31)
Mean (SEM)	88.31 (1.400)	62.72 (3.432)
SD	7.920	19.108
Median	89.81	65.79
Min, Max	62.9, 98.7	28.7, 95.5
LS means (SEM)	88.28 (2.599)	62.76 (2.639)
Difference between EUR-1008 and Placebo		-25.52
95% CI		(-31.73, -19.32)
P value		<0.001

Source: EUR-1008-M Study Report (Page 63, Section 11.4.1, Table 6; Section 14, Table 14.4.1)

The results of the primary endpoint show a statistically significant mean change in CFA in patients treated with EUR-1008 as compared to patients on placebo (no treatment). The clinical significance of a mean change in CFA of 25% is challenging to interpret. In the EUR-1008 clinical development program, the primary endpoint results were analyzed in conjunction with the changes in CFA for individual patients (see Table A in Appendix). This concept was discussed with the Sponsor at the pre-NDA meeting. See Section 2.5 for complete description.

5.3.1.11.7.2 Additional Analyses of the Primary Endpoint

This Reviewer performed additional analyses of the primary endpoint, including analyses of the change in CFA by no-treatment (placebo) CFA, by treatment sequence, by gender, and by age.

Analysis by No-Treatment CFA

A widely accepted definition of severe EPI is patients who have a CFA less than or equal to 40% on no treatment. In addition, treatment effect has been reported to be more pronounced in patients with lower no-treatment CFA. . The medical literature notes that in the most severely affected patients an increase from baseline in CFA of 30% represents a clinically meaningful change, thus, this subgroup of patients was analyzed separately.

There were five patients in the severe category. They had a mean placebo (no-treatment) CFA of 35% and a mean change in CFA on EUR-1008 of 47%. All but one of the most severely affected patients had an increase in CFA greater than 50%. Patient 105801 had an increase in CFA of 25%. This Reviewer looked for reasons to explain the apparent decreased efficacy for this particular patient relative to the other severely affected patients; however, no etiology was identified. Thus, in general, the most severely affected patients demonstrated the greatest response to treatment with EUR-1008. The magnitude of the change (mean change 47% in this group, and >50% in most of the patients) was a clinically meaningful result. Individual results for patients with CFA<40 on placebo are tabulated below in Table 7.

Table 7: Patients with No-Treatment CFA< 40

Patient	Placebo	EUR-1008	Change in CFA
103804	(b) (4)	(b) (4)	(b) (4)
112803			
102802			
108801			
105801			
Mean	**35**	**82**	**47**
Median	**38**	**84**	**51**
Min, Max	(b) (4)	(b) (4)	(b) (4)

For the subgroup of patients (N=21) who had moderate EPI (arbitrarily defined by this Reviewer as a no-treatment CFA greater than 40 and less than 80), the increase in CFA following EUR-1008 treatment (mean change in CFA of 26) was not as pronounced as seen in the patients with severe EPI. This result is not unexpected as these moderately affected patients have less of a capacity to respond, since they started at a higher no-treatment level. In general, there was a gradation in treatment responses with larger increases in CFA for patients with placebo CFAs at the low end, and smaller increases for higher placebo CFA levels. After treatment with EUR-1008, all but one patient had a CFA level > 80, so overall, patients had a good clinical response. See Table 8 for individual patient results.

Table 8: Placebo-Treatment CFA of >40 and < 80

Patient	Placebo	EUR-1008	Change in CFA
101804	(b) (4)	(b) (4)	(b) (4)
103802			
109806			
103801			
116802			
105805			
105804			
118803			
109803			
109805			
105807			
112805			
101802			
105806			
115803			
103803			
118802			
112804			
115801			
105803			
106801			
Mean	**62**	**88**	**26**
Median	**66**	**89**	**23**
Min, Max	(b) (4)	(b) (4)	(b) (4)

For the subgroup of patients who had mild EPI (N=6) (arbitrarily defined by this Reviewer as a no-treatment CFA greater than 80), the mean change in CFA was 1%. The small increase in CFA observed in this subgroup of patients is not unexpected given that these patients had high CFAs on no-treatment (4 patients with a CFA >90). Most of the patients in this subgroup did have a small improvement of CFA following EUR-1008 treatment; all but one patient had a EUR-1008 CFA >94%. This Reviewer looked for a reason for the one patient's decrease in CFA with EUR-1008 treatment; however, no etiology was discovered. See Table 9 for individual patient results.

Table 9: Placebo CFA> 80

Patient	Placebo	EUR-1008	Change in CFA
101805	(b) (4)	(b) (4)	(b) (4)
109804			
115802			
112801			
108802			
116801			
Mean	**93**	**94**	**1**
Median	**94**	**94**	**1**
Min, Max	(b) (4)	(b) (4)	(b)

Overall, the additional efficacy analysis of change in CFA by no-treatment CFA in Study 1008-M showed that the increase in CFA on EUR-1008 treatment is greatest in the most severely affected patients. The patients who had a higher no-treatment CFA showed smaller increases in CFA after treatment with EUR-1008.

The inverse relationship between low no-treatment CFA and change in CFA (the lower the value initially, the higher the increase) is critical to the efficacy of the study. The patients who were the most severely affected gained the most benefit by having had an increase in CFA of at least 30% (mean change in CFA of 47%); this percentage increase was defined by the medical literature as a clinically meaningful result. Most other patients also had increases in CFA following treatment with EUR-1008.

These results above support the approval of EUR-1008 for the treatment of EPI; treatment with EUR-1008 is beneficial to most patients. The treatment affect is variable; however, it follows a trend that the greatest change in CFA is observed in the patients with the lowest no-treatment CFA.

Analysis by Treatment Sequence

The efficacy results were analyzed according to sequence. Patients in sequence 1 were randomized to receive placebo during the first treatment period followed by EUR-1008 during the cross-over treatment period. There were similar numbers of patients randomized to each sequence (15 in sequence 1; 17 in sequence 2). The mean change in CFA was also similar for patients in each sequence, 23% for sequence 1 and 27% for sequence 2. The Statistical Reviewer also analyzed the efficacy results according to sequence and did not note any visible impact on efficacy outcomes. See Tables 10 and 11.

Table 10: Sequence 1 Patients

	Placebo	EUR-1008	Change in CFA
108802	(b) (4)	(b) (4)	(b) (4)
103804			
112803			
102802			
109806			
116802			
118803			
109803			
101802			
105806			
115801			
105803			
109804			
115802			
116801			
Mean	**63**	**87**	**23**
Median	**66**	**87**	**20**
Min, Max	(b) (4)	(b) (4)	(b) (4)

Table 11: Sequence 2 Patients

Patient	**Placebo**	**EUR-1008**	**Change in CFA**
108801	(b) (4)	(b) (4)	(b) (4)
105801			
101804			
103802			
103801			
105805			
105804			
109805			
105807			
112805			
115803			
103803			
118802			
112804			
106801			
101805			
112801			
Mean	**62**	**90**	**27**
Median	**66**	**92**	**25**
Min, Max	(b) (4)	(b) (4)	(b) (4)

The above analysis supports the fact that the order of treatment (placebo to EUR-1008 or EUR-1008 to placebo) did not affect the efficacy of EUR-1008.

Analysis by Gender, Age and Race

The efficacy results were also analyzed by gender and by age; there were too few non-Caucasians to analyze by race (32 of 34 patients were Caucasian; 94%). The efficacy results were similar for both males and females, with mean change in CFA equal to 25% and 24%, respectively (results not shown, see Tables B and C in the Appendix).

There were no meaningful differences in mean change in CFA with respect to age. Patients were divided into three age subgroups (7-11; 12-16; ≥17) by this reviewer. All patients from ages 7 to adult had mean changes in CFA by age subgroups from 22 to 28%. There were no clinically meaningful differences seen in response to EUR-1008 treatment by age sub groupings The minor differences between age subgroups could be due to the small number of patients in each age subgroup, since a single patient's result could skew the average CFA in that subgroup. See tables D, E, and F in Appendix for full details.

The primary efficacy endpoint was the comparison of the coefficient of fat absorption (CFA) after administration of EUR-1008 versus placebo. The overall results showed that a clinically meaningful and statistically significant increase in CFA was demonstrated in the efficacy analysis population, with an overall mean change in CFA of 25% ($p < 0.001$; 95% CI [-31.7, -19.3]). Unplanned additional and subgroup analyses showed that factors such as treatment sequence, gender, and age did not appear to affect efficacy; however, patients with lower placebo-treatment CFA tended to have a better response to treatment with EUR-1008.
As expected from the published medical literature with treatment with other PEPs, the patients in this study who were the most severely affected gained the most benefit by having had an increase in CFA of at least 30% (mean change in CFA of 47%): this percentage increase was defined by the medical literature as a clinically meaningful result. Conversely, patients with higher placebo CFA had a lesser responses to EUR-1008 treatment.

5.3.1.11.7.3 Secondary Efficacy Analysis

There were several secondary efficacy endpoints in this study. These endpoints evaluated other factors that may help to support the results of the primary efficacy analysis; however, these endpoints are not suitable for labeling. Many of the secondary efficacy endpoints analyzed were too subjective or too short-term (weight/BMI, serum levels of cholesterol and fat-soluble vitamins, clinical symptoms of EPI, and Quality of Life questionnaires) and others (CNA) had no clinically definable change that was clinically meaningful.

Coefficient of Nitrogen Absorption (CNA)

A major secondary endpoint was the comparison of CNA after administration of EUR-1008 versus placebo.

The results showed that the mean CNA for EUR-1008 and placebo were 87% and 66%, respectively. The mean change in CNA was 21.5%, and this was a statistically significant change. (See Table A1electronically scanned and copied from Sponsor). These results were confirmed by FDA Statistical Reviewer. Most patients had an increase in CNA after treatment

with EUR-1008. In general, patients with the lowest placebo CNA showed the most improvement. The individual values of CNA are represented in Table G in the Appendix.

Table 12: ANOVA Model Results of Coefficient of Nitrogen Absorption (CNA, %)

	EUR-1008 (N=32)	Placebo (N=31)
Mean (SEM)	87.25 (1.129)	65.71 (2.912)
SD	6.387	16.211
Median	87.84	69.75
Min, Max	68.6, 98.7	35.9, 93.5
LS means (SEM)	87.17 (2.179)	65.67 (2.213)
Difference between EUR-1008 and Placebo		-21.50
95% CI		(-26.85, -16.14)
P value		<0.001

Source: EUR-1008-M Study Report (Page 64, Section 11.4.2.1, Table 7; Section 14, Table 14.4.2)

These results are supportive of a positive enzymatic effect of PEP treatment; however, a clinically meaningful change in CNA has not been established, so the clinical relevance of these results is not known.

Weight/BMI

A secondary endpoint was the comparison of weight/BMI from Screening to End of Study between the EUR-1008 and placebo treatment periods. The mean (SD) weight during the study was approximately 51 kg (14.8); the mean BMI (SD) was approximately 20.5 (2.9). The results showed that there were no clinically significant changes in mean weight and BMI from Screening to End of Study and between treatment periods; however, there were two notable AEs for changes in weight in individual patients described below.

The results for change in weight were notable in that there were two patients, both approximately 16 years of age, who experienced clinically significant weight loss (AEs), each during two separate treatment periods.

- Patient 103801 had a 3 kg weight loss while being treated with placebo during the randomization treatment period; his weight increased by 2 kg after treatment with EUR-1008 in the open-label normalization period 1. This patient had a mild weight loss (less than 1 kg) during treatment with EUR-1008 in the crossover treatment period, which resolved at the End of Study visit. The investigator considered both events to be possibly related to study drug.

- Patient 103802 experienced two AEs of mild weight loss: one while being treated with placebo during the randomization treatment period 1 and the other while being treated with EUR-1008 during the crossover treatment period.

It is not unexpected that patients would lose weight during placebo treatment, nor during change in PEP treatment if the treatment was not optimizing the malabsorption symptoms. Sixteen year old boys with higher BMIs are probably more vulnerable to weight loss since they have high caloric needs. These weight changes do not appear to be directly attributable to EUR-1008 treatment.

Serum Levels of Cholesterol and Fat-soluble Vitamins

Another secondary endpoint was the comparison of serum levels of cholesterol and fat-soluble vitamins from Screening to End of Study between the EUR-1008 and placebo treatment periods. There were no notable changes in serum levels of cholesterol and fat-soluble vitamins between screening and either of the treatment periods or End of Study.; however, no substantial changes in serum levels of cholesterol and fat soluble vitamins are expected from this short-term study.

Clinical Symptoms of EPI (stool frequency, stool consistency, bloating flatulence and pain) and Quality of Life Questionnaires

The final secondary endpoint was the comparison of clinical symptoms of EPI and Quality of Life questionnaires from Screening to End of Study between the EUR-1008 and placebo treatment periods. The Sponsor reported that there were statistically significant differences in mean stool frequency (EUR-1008 mean of 1.76 vs. placebo mean of 2.66) and consistency (EUR-1008 had more hard, formed stool) between the treatment groups. This Reviewer believes that fractional increases in stool number and subjective assessments of stool consistency may have statistical significance; however, these minor differences are not clinically meaningful and cannot be used to support labeling.

There were no notable changes in the parameters used to assess quality of life.

These secondary efficacy variables were difficult to analyze accurately given the multiple variables involved and nature of the underlying disease. Most secondary endpoints were subjective and assessed without using validated endpoint measures. Study 1008-M was of short duration and had a disproportionate amount of EUR-1008 treatment time, which made the analysis of treatment differences more difficult.

Thus overall, given the subjective nature of the analyses of the secondary efficacy variables, and the lack of clinical relevance, these results are not sufficient to support labeling.

5.3.1.11.8 Review of Safety

5.3.1.11.8.1 Deaths and Serious Adverse Events (SAEs)

There were no deaths reported during study EUR-1008-M. There were two serious adverse events (SAEs) reported by two patients, as follows:

- Patient 101805 had a lung infection for which he was admitted to the hospital and successfully treated with antibiotics.

- Patient 116801 (who had a previous history of hemoptysis) had an episode of severe hemoptysis for which he was hospitalized. No treatment was reported for the SAE, and it was recorded as resolved after 10 days.

These events were assessed by the investigators to be probably secondary to each patient's underlying disease of Cystic Fibrosis, and were not attributed to treatment with study medication. This Reviewer is in agreement with the investigators' assessments.

5.3.1.11.8.2 Common Adverse Events

Patients in this study were exposed to EUR-1008 for a longer period of time than the exposure to placebo (29.7 days vs. 6.3 days). Thus, adverse events may appear to be more prevalent during the EUR-1008 treatment periods due to this disparity.

There were a total of 160 AEs reported during the study, which occurred in the safety population (N=34) of Study EUR-1008-M. One hundred seventeen occurred during EUR-1008 treatment and 43 occurred during placebo treatment. Although patients reported more AEs during EUR-1008 treatment than during placebo treatment, this is likely due to the longer exposure to EUR-1008 than to placebo. Except for more headaches during EUR-1008 treatment, there were no obvious differences in the types of AEs reported during either treatment. It is unclear why there is an imbalance in headaches between treatment groups; however, the small study size makes it difficult to interpret these results.

The most commonly reported AEs were in the gastrointestinal and respiratory systems as would be expected in this patient population. The most commonly reported AEs were abdominal pain (44% of patients overall), flatulence (27%), headache (24%) and abdominal distension (24%). Careful review of the adverse event datasets by this Reviewer did not reveal any obvious or noteworthy safety signals, and in general, the AE profile reported in this study is similar to the side-effect profile of PEPs as reported in the medical literature. See Table 13 below for all AEs reported in $\geq$ 5 % of the safety population (i.e., reported by 2 or more patients; $\geq$5% of patients). (For a complete listing of the AEs reported in this study, please see table H in the Appendix.)

Table 13: Adverse Events Reported by ≥ 5% of Patients (2 or more patients)

System Organ Class, Disorders	Preferred Term	All N=34 (%)	EUR-1008 N=34 (%)	Placebo N=32 (%)
Gastrointestinal	Abdominal pain	15 (44)	9 (27)	6 (19)
	Flatulence	9 (27)	6 (17)	3 (9)
	Abdominal distension	8 (24)	5 (15)	3 (9)
	Steatorrhea	6 (17)	2 (6)	4 (13)
	Abdominal pain upper	5 (15)	2 (6)	3 (9)
	Abnormal feces	5 (15)	2 (6)	3 (9)
	Frequent bowel movements	4 (13)	2 (6)	2 (6)
	Nausea	3 (9)	2 (6)	1 (3)
	Abdominal discomfort	2 (6)	2 (6)	0
	Dyspepsia	2(6)	2 (6)	0
	Vomiting	2(6)	2 (6)	0
General disorders and administration site conditions	Early satiety	2(6)	2 (6)	0
	Pyrexia	2(6)	2 (6)	0
Injury, poisoning and procedural complications	Contusion	2(6)	2 (6)	0
	Injury	2 (6)	2 (6)	0
Investigations	Weight decreased	4 (13)	2 (6)	2 (6)
	Pulmonary function test decreased	2 (6)	2 (6)	0
Nervous system	Headache	8 (24)	8 (24)	0
	Dizziness	2 (6)	1 (3)	1 (3)
Respiratory, thoracic and mediastinal	Cough	4 (13)	4 (13)	0
	Crackles lung	2 (6)	1(3)	1(3)
	Nasal congestion	2 (6)	2 (6)	0

Since the total exposure to EUR-1008 was longer than the total placebo exposure, a separate analysis of the adverse events reported during the two double-blind treatment periods (treatment period and cross-over treatment period) only was performed (see Table 14). Due to the small study size, the short duration of the DB treatment periods (6 to 7days), and as only a few AEs were reported by more than one patient, it is difficult to draw definitive conclusions from the analysis. However, several gastrointestinal complaints (steatorrhea, abnormal feces, frequent BM, upper abdominal pain) seemed to be more commonly reported in the placebo group, and headache was more commonly reported in the EUR-1008 group. The etiology of the imbalance in gastrointestinal complaints is expected as the patients receiving placebo have untreated EPI. There were no discontinuations from the study secondary to headache, or any other AE. These AEs were also comparable to the AEs observed in previous studies of other PEPs; GI complaints were most common and headaches were also prevalent.

Table 14: AE's During Treatment Period and Crossover Treatment Period

System Organ Class, Disorders	Preferred Term	EUR-1008 N=34	Placebo N=32
Gastrointestinal	Abdominal pain	4 (12)	6 (19)
	Flatulence	2 (6)	3(9)
	Abdominal distension	1 (3)	3 (9)
	Abnormal feces	1 (3)	3 (9)
	Frequent BM	1(3)	3(9)
	Upper abdominal pain	1(3)	3(9)
	Nausea	1(3)	1(3)
	Abdominal discomfort	1(3)	0
	Abdominal tenderness	1(3)	0
	Constipation	1(3)	0
	Vomiting	1(3)	0
	Steatorrhea	0	4 (12)
	Abnormal bowel sounds	0	1(3)
	Infrequent BM	0	1(3)
Nervous system	Headache	5(15)	0
	Dizziness	0	1(3)
Investigations	Weight decreased	1(3)	1(3)
	Weight loss	1(3)	0
General disorders and administration site conditions	Early satiety	2 (6)	0
	Chest pain	1(3)	0
	Mucosal edema	1(3)	0
	Pyrexia	1(3)	0
Injury, poisoning and procedural complications	Contusion	2 (6)	0
	Anal injury	1(3)	0
	Injury	1(3)	0
	Fall	0	1(3)
Metabolism and nutrition	Anorexia	0	1(3)
Respiratory, thoracic and mediastinal	Cough	2(6)	0
	Crackles in lung	1(3)	1(3)
	Dysphonia	0	1(3)
Infections and infestations	Otitis externa	0	1(3)
Reproductive system and breast	Vaginal burning sensation	0	1(3)
Skin and subcutaneous tissue	Rash	1(3)	0
Vascular	Hematoma	1(3)	0

5.3.1.11.8.3 Safety Summary

Exposure to EUR-1008 (with dosages of 4,000-5,000 lipase units/kg/day) during the study was similar to what is currently encountered for PEP treatment of CF patients in clinical practice. The mean days of exposure to EUR-1008 was approximately four times longer than that for placebo (30 days versus 6 days). There were no deaths during study EUR-1008 and the two SAEs reported during the study (lung infection and hemoptysis) were assessed by the investigators to be related to the patients' underlying disease (CF). No patients discontinued from the study due to an AE or laboratory abnormality. There were no clinically significant

abnormalities in laboratory data; individual patient vital signs and physical exams remained stable throughout the study.

For the duration of the study, there were more AEs observed during treatment with EUR-1008 versus placebo; however, this imbalance may be secondary to the longer exposure of EUR-1008. When only the DB treatment periods were compared, the types of AEs as well as the number of patients who experienced at least one AE were similar between treatment periods. The AEs observed were consistent with the underlying disease of the patients (mostly in the gastrointestinal and respiratory organ systems), and most were mild or moderate in severity. The most commonly reported AEs were abdominal pain (44%), flatulence (27%), and headache and abdominal distension (24% each). Careful review of the adverse event datasets by this Reviewer did not reveal any obvious or noteworthy safety signals, and in general, the AE profile reported in this study is similar to the side-effect profile of PEPs as reported in the medical literature.

5.3.1.12 Summary and Conclusions for Study EUR-1008-M

The primary endpoint of the pivotal study, EUR-1008-M, was met. Treatment with EUR-1008 resulted in a statistically significant increase in absorption of fat (increase in CFA) compared to placebo. The most severely affected patients (placebo CFA <40%) demonstrated the greatest response to treatment with EUR-1008 (mean CFA increase $\geq$30%), which was clinically meaningful. Subgroup analyses showed that factors such as gender and age did not appear to affect efficacy. The efficacy of EUR-1008 was demonstrated in adults and pediatric patients 7 years or older.

Exposure to EUR-1008 during the study was similar to what is currently encountered for PEP treatment of CF patients in clinical practice. The safety profile of EUR-1008 was acceptable and was consistent with the safety profile reported for other PEPs.

Thus overall, the results of the pivotal trial demonstrate that CF patients who are treated with EUR-1008 have objective and subjective improvement of their clinical symptoms of EPI, and that EUR-1008 is reasonably well tolerated by this patient population. These results support the approval of EUR-1008 for the treatment of EPI in this patient population.

5.3.2 EUR-1009-M

5.3.2.1 Study Design

The supportive study, EUR-1009-M, was a multicenter, open-label, non-randomized, multiple-dose, single-treatment study evaluating the efficacy and safety of EUR-1008 in 19 patients, ages 1 to 6 years old, with confirmed diagnosis of CF and EPI. The study was designed to compare measures of fat malabsorption before (while on usual PEP treatment) and after oral administration of EUR-1008.

The study design consisted of: a screening period (1 to 14 days wherein patients continued on their current PEPs), a dose-stabilization period (7 days wherein patients were titrated to an appropriate dose of EUR-1008), and a treatment period (7 days wherein patients remained on a stable dose of EUR-1008). There were no wash-out periods between each of the three study periods; thus, patients remained on some PEP for the duration of the study. See Study Design below.

Study Design EUR-1009-M

- Screening Period (1-14 days)
  - Continued on current PEPs, determine eligibility

- Dose-Stabilization Period (7 days)
  - Transition from usual PEP treatment to EUR-1008 and titration of EUR-1008 to appropriate dose

- Treatment Period (7 days)
  - Continuation of stable EUR-1008 dose

5.3.2.2 Study Objectives

The objectives of the study were to evaluate the short-term safety and effectiveness of EUR-1008 as compared to other PEP treatments in patients with EPI due to CF.

5.3.2.3 Patient Population

5.3.2.3.1 Key Inclusion Criteria

Patients were eligible for study participation if they were males or females six years of age or younger, and:

- Had confirmed diagnoses of CF - Two clinical features consistent with CF *and* genotype consistent with CF or sweat chloride concentration > 60 mEq/L, and
- Had confirmed diagnosis of EPI - by documented fecal elastase < 100 micrograms/g stool.
- Had a need of *de novo* treatment with PEPs or be able to be switched from existing treatment

5.3.2.3.2 Key Exclusion Criteria

Patients were excluded from study participation if they had any of the following exclusion criteria:

- History of fibrosing colonopathy.
- Had recent illness involving acute systemic administration of antibiotics within previous four weeks or acute steroid use within previous two weeks.

- History of solid organ transplant or significant bowel surgery.
- Use of immunosuppressive drugs.
- Use of enzyme preparation greater than 10,000 lipase units per kg/day.

5.3.2.4 Concomitant Medications

PEPs other than EUR-1008 were not allowed during the study.

Patients who were successfully screened must have stopped using any of the following medications/preparations prior to 12:00AM on Study Visit 2 and until the end of the study: PPIs, H2 blockers or other agents that alter gastric pH, motility agents, buffering agents, laxatives, synthetic fat substitutes, and fat-blocking nutritional supplements. All other medications were permitted for use during the study, and were recorded on the CRFs.

5.3.2.5 Study Visits and Procedures

All of the study visits took place in an outpatient setting. The study visits and procedures are summarized in Table 15 (electronically copied and reproduced from the sponsor's submission).

Table 15: Schedule of Study Assessments

Procedures	Screening Days 1-4	Dose-Stabilization Period Days 5-11	Treatment Period Days 12-19[a]	
Visit	1	2	3	4
Day	1	5[b]	12	19
Informed consent	X			
Medical and medication history	X	X		
Complete physical examination[c]	X			X
Abbreviated physical examination[d]		X	X	
Blood for serum chemistry and hematology and urine for urinalysis and uric acid levels[e]	X[f]			X[f]
Blood for cholesterol (high and low density) and vitamins A, E, and K[g]	X[f]			X[f]
Diary maintenance, including diet[h, i]	X	X	X	X
Clinical symptoms of EPI[h,i]	X	X	X	X
Assessment of DIOS	X	X	X	X
Stool collection (elastase)[j]	X			
Stool collection for fecal fat	X		X[k]	X[k]
AE and concomitant medication review		X	X	X
Study drug dispensed[l]		X	X	

AE = adverse event, DIOS = distal ileal obstruction syndrome, EPI = exocrine pancreatic insufficiency, PIVKA II = des-carboxylated prothrombin protein induced by absence of vitamin K

[a] The last day of study treatment was Day 18 and the End of Study was Day 19.

[b] May have been earlier than Day 5 if all screening assessments were available for review.

[c] Assessment of body systems, height, weight, vital signs.

[d] Weight, vital signs, and abdominal examination only.

[e] If a patient terminated the study early, blood and urine samples were collected.

[f] Patients fasted for at least 6 hours, if possible, prior to these blood draws.

[g] PIVKA II was the test performed to determine vitamin K deficiency levels.

[h] A diary card was issued at Screening; subsequently, at each visit, the completed diary card was returned to the clinic and a new card issued.

[i] A diary card was issued to the parent/legal guardian (at Screening and each visit) and maintained a record of all food consumed, medications taken, potential AEs, and symptoms of EPI. Clinical symptoms of EPI included stool frequency, stool consistency (hard, formed/normal, soft, watery, or overt diarrhea), oil or grease in the stool, and/or macroscopically evident blood in stool.

[j] If the patient did not have previous data on fecal elastase, a stool collection for the analysis of fecal elastase (<100 µg/g) was done at Screening only.

[k] Stool collection for total fat was done on Day 11 (for Day 12) and Day 18 (for Day 19). Samples were collected at home, frozen, and taken to the clinic the next day for analysis.

[l] The first dose of the day on Days 5 and 12 was given at the clinic. Additional drug supplies were given to the parent/legal guardian for administration to the patient at home.

5.3.2.6 Randomization and Controls

This study was an open-label, non-randomized, uncontrolled study, and all patient received active treatment with EUR-1008. No blinding procedures were used, and all patients, caregivers, and study personnel were aware that patients were receiving treatment with EUR-1008.

5.3.2.7 Study Medication Dose Selection, Dispensing, and Compliance

The optimal dose of EUR-1008 was determined during the dose stabilization period, and was continued during the treatment period. Patients began treatment using an approximated dose of EUR-1008, which took into account the patient's body weight and the previous enzyme dose from their usual pre-study PEP treatment. The actual dose of EUR-1008 was titrated based on the patient's malabsorption symptoms.

The study used only the 5,000 lipase units/capsule strength of EUR-I008, which could be opened and the contents sprinkled on food if necessary. Doses of PEPs were not to exceed 2,500 lipase units/kg/meal or a total dose of 10,000 lipase units/kg/day.

Each patient received two treatment packs (on Day 5 and Day 12) that contained sufficient medication at the maximum allowable dose to complete a particular treatment period. Compliance with the doses of study drug given was monitored by the study coordinator. During the dose-stabilization period and treatment phase, a parent/legal guardian recorded on diary cards each dose of EUR-1008 used with each meal or snack.

5.3.2.8 Efficacy and Endpoint Measures

All patients who received at least one dose of study drug were included in the efficacy analysis and safety analysis populations.

5.3.2.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the percentage of "responders" after one and two weeks of treatment. Responders were defined as patients without steatorrhea (<30% fecal fat content) AND without signs/symptoms of malabsorption. The lack of steatorrhea was assessed from the fecal fat readings after the dose stabilization period (EUR-1008/Day 11) and after the treatment period (EUR-1008/Day 18) compared with baseline (current PEP). "Without signs/symptoms of malabsorption" was defined as a patient having all of the following criteria:

- Normal stool consistency without blood or oil/grease.
- No pain.
- None/mild bloating.
- None/mild flatulence.

In this study, fecal fat content was determined by spot fecal fat testing. The sponsor felt that 72-hour, in-hospital stool collection for fecal fat would be too challenging in this younger patient

population. An agreement between the Sponsor and the Division allowed spot fecal fat testing as an alternative. See Section 2.5. The quantity of fat in stool samples was determined by nuclear magnetic resonance (NMR) spectrometry.

5.3.2.8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints were:

- To compare nutritional status (weight change), stool frequency and consistency, incidences of bloating, pain and flatulence, and incidences of visible blood and grease/oil in stool before (at screening while on usual PEP treatment) and after treatment with EUR-1008.

- To compare clinical symptoms before and after treatment with EUR-1008.

5.3.2.9 Statistical Considerations

This is an open-label, uncontrolled study, and endpoints are considered to be descriptive only. This study is being used as a supportive study for the treatment of patients six years of age and younger and no formal statistical comparisons will be made.

5.3.2.10 Protocol Amendments

A list of protocol amendments is found in volume 18. The most notable amendment increased the screening period by 10 days. Most of the protocol amendments were minor and did not impact the review.

5.3.2.11 Study Results

5.3.2.11.1 Demographics

There were 19 children between the ages of 1 and 6 years enrolled in Study 1009-M. There was a higher percentage of males than females (63% vs. 37%, respectively). Almost 50% of patients were between the ages of 1 and 3 years, approximately 40% were 4 and 5 years old, and approximately 15% were age 6 years old; however, there were no patients less than 1 year of age enrolled. Almost all patients were of non-Hispanic descent (90%), and all patients were Caucasian. Since CF is a disease predominantly of Caucasians, the study population is representative of the CF population. See Table 16 for a summary of the demographic data for patients enrolled in Study 1009-M.

Table 16: Demographics of EUR-1009-M

Demographic Variable	**N=19**
Age (years)	Mean (SD): 3.9 (1.6) Median: 4.2 Range: 1-6
Age categories	<1: 0 1-3: 9 (47%) 4-5: 7 (37%) 6: 3 (16%)
Gender	Male: 12 (63.2%) Female: 7 (36.8%)
Ethnicity	Hispanic: 2 (10.5%) Non Hispanic: 17 (89.5%)
Race	Caucasian: 19 (100%)
Duration (yrs) of CF diagnosis	Mean (SD): 3.3 (1.5) Range: 1-6

5.3.2.11.2 Patient Disposition

The study was conducted at ten clinical centers in the United States; one site screened but did not enroll any patient. The minimum and maximum number of patients enrolled per site was one and four, respectively. All patients completed the study; however, one patient did not provide an end of treatment fecal fat sample.

5.3.2.11.3 Concomitant Medications

The most commonly reported concomitant medications were multivitamins (100% of patients), dornase alfa (53%), and salbutamol (53%). In addition, eleven patients listed an enzyme preparation as a concomitant medication because they were taking their usual PEP treatments during the Screening period of the study, which was stopped on the first day of EUR-1008 treatment.

It is likely that many patients with CF use the medications mentioned above; thus, the medications taken by the study population would be representative of the medications that will be used by the intended population post approval.

5.3.2.11.4 Compliance

Compliance with the doses of study drug given was monitored by the study coordinator. During the dose-stabilization period and treatment phase, a parent/legal guardian recorded on diary cards each dose of EUR-1008 used with each meal or snack.

5.3.2.11.5 Efficacy Results

5.3.2.11.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the percentage of "responders" after one and two weeks of treatment. Responders were defined as patients without steatorrhea (<30% fecal fat content) AND without symptoms of malabsorption. Responders have:

- Fecal fat content < 30%; ***and***

- No signs/symptoms of malabsorption defined as:
    - Normal stool consistency without blood or oil/grease.
    - No pain.
    - None/mild bloating.
    - None/mild flatulence.

Responders at Screening represent the efficacy of prior PEP treatment. Responders at Visit 3 represent the efficacy of EUR-1008 after seven days of dose stabilization to an effective dose, and responders at End of Treatment represent the efficacy of EUR-1008 after seven additional days of treatment at an effective dose.

At Screening there were 10 responders (53%), after the dose-stabilization period (Visit 3) there were 13 responders (68%), and at end of treatment there were 11 responders (58%). Please see Table I in Appendix for fecal fat values and responder status per patient and study visit.

When maintenance of response was analyzed, many patients who were Screening responders continued to be responders during Visit 3 (N=9), and some patients (N=4) continued to be responders throughout the entire study. See Table 17.

Table 17: Responder Maintenance

Patient	Screening	Visit 3	End of Study
102901	X[1]	X	O
103901	X	X	X
104902	X	X	O
104903	X	X	X
106901	X	X	X
106904	X	X	X
110901	X	X	O
113901	X	X	O
113902	X	X	O
116902	X	O	O
101903	O[2]	X	X
102902	O	X	X
103902	O	X	X
115901	O	X	X
101902	O	O	X
101904	O	O	X
110901	O	O	X
101901	O	O	O
109902	O	O	O

[1]X= Responder
[2]O = Non-Responder

Many patients at Screening, Visit 3 and End of Study were responders: several patients maintained a response throughout the entire study. Only two patients were non-responders during the entire study. Given that the patients EPI symptoms were controlled on their previous PEP, the findings are not unexpected. These results support the premise that patients may be successfully changed from treatment with one PEP to treatment with EUR-1008 and continue to respond to therapy. Thus overall, the primary efficacy endpoint results are supportive of the efficacy of EUR-1008 in younger patients.

5.3.2.11.5.2 Additional Efficacy Analysis

Assessment of Changes in Fecal Fat

Relying only on objective data (as opposed to subjective symptoms), an assessment of changes in fecal fat from Screening was performed by this Reviewer. This analysis showed that mean fecal fat percentages were similar for each study visit (approximately 26%). Since patients were studied while continued on their current PEP regimen, many had Screening (Baseline) fecal fat percentages less than 30, and thus, substantial changes in mean fecal fat percent were not seen. Large changes in mean fecal fat values were not expected as these patients' EPI symptoms were presumably controlled on their previous PEP. See Table 18 below.

Individual patient results for fecal fat changes from Screening to End of Study were also analyzed by this Reviewer. Most patients had changes from visit to visit within approximately 10%, either an increase or a decrease. Three patients had a greater than ten percent increase

(14% to 18%) in fecal fat percentage. One patient had a large (28%) increase in fecal fat percent at Visit 3; however, by End of Study, the increase in fecal fat percent was six. No clear etiology was established to explain these outliers. It is additionally noted by this Reviewer that there were several patients who had low fecal fat percentages, however, they were not classified as responders. (See Table I in Appendix)

Table 18: Fecal Fat Content (%)

Visit	Actual measurement N=19	Change from Screening N=19
Screening	Mean 25 (SD=6.1) Range 17-38	
After Dose Stabilization Period	Mean 27 (SD=7.5) Range 17-46	Mean 2.2 (SD=9) Range -13-28
End of Treatment	Mean 27 (SD=6.6) Range 17-39	Mean 2.3 (SD=8.8) Range -12-18

On average, patients had fecal fat percentages less than 28 at Screening**, a**fter the Dose Stabilization Period (Visit 3), and at End of Treatment (End of Study). This finding is supportive of the use of EUR-1008 in continuing to control fecal fat content (steatorrhea) in a younger population with EPI.

5.3.2.11.5.3 Efficacy Conclusions

The supportive study, EUR-1009-M, showed that the primary efficacy results obtained at Screening were similar to the results obtained after treatment with EUR-1008. Many patients at Screening, Visit 3 and End of Study were responders and several patients maintained a response throughout the entire study; there were only two patients who were not responders at any time during the study. On average, patients had fecal fat percentages less than 28 at Screening, after the Dose Stabilization Period (Visit 3), and at End of Treatment (End of Study).

These results support the premise that patients may be successfully changed from treatment with one PEP to treatment with EUR-1008 and continue to respond to therapy. Study EUR-1009-M showed that there was a persistent response to treatment with EUR-1008 for younger patients. Thus, these results can be used as supportive evidence of efficacy, and allow for the extrapolation of the efficacy results obtained in Study EUR-1008-M to a younger patient population.

5.3.2.11.6 Safety Results

5.3.2.11.6.1 Deaths and Serious Adverse Events (SAEs)

There were no deaths in Study 1009-M. There was one reported SAE of upper respiratory tract infection. Patient 102902 was hospitalized for four days for a respiratory infection and successfully treated with antibiotics. The SAE was thought by the investigator to be a concurrent illness and not related to study drug.

5.3.2.11.6.2 Common Adverse Events

All patients were exposed to EUR-1008 for 14 days. The mean dose taken during the dose stabilization period was 5,094 lipase units/kg/day, and during the treatment period was 5,417 lipase units/kg/day.

A total of 51 AEs were reported in 13 patients during Study-1009-M. As expected, the gastrointestinal system had the most reported AEs, and the most commonly reported AEs were abdominal pain (reported by 26% of patients) and steatorrhea (16%). See Table 18 for incidences of all AEs.

Table 18: Study 1009-M Incidence Table, All Adverse Events

System Organ Class, Disorders	Preferred Term	Patient Events
	N=19 (%)	N=19 (%)
Gastrointestinal	Abdominal pain	5 (26)
	Steatorrhea	3 (16)
	Feces discolored	2 (11)
	Flatulence	2 (11)
	Vomiting	2 (11)
	Abdominal discomfort	1 (5)
	Abdominal distension	1 (5)
	Diarrhea	1 (5)
General disorders and administration site conditions	Pyrexia	3 (16)
	Upper respiratory tract infection	2 (11)
	Bronchitis	1 (5)
Infections and infestations	Sinusitis	1 (5)
Injury, poisoning and procedural complications	Contusion	1 (5)
	Injury	1 (5)
	Sunburn	1 (5)
Metabolism and nutrition	Anorexia	1 (5)
	Decreased appetite	1 (5)
Nervous system	Headache	1 (5)
Psychiatric	Insomnia	1 (5)
Respiratory, thoracic and mediastinal	Nasal congestion	2 (11)
	Rhinorrhea	2 (11)
	Cough	1 (5)
	Paranasal sinus hypersecretion	1 (5)
Blood and lymphatic system	Lymphadenopathy	1 (5)
Eye	Lacrimation increased	1 (5)

The majority (34/51, 67%) of AEs were considered by the investigator to be not related to study drug. Five patients reported a total of 17 AEs that were considered possibly related to study drug. Of these, the most common AEs were abdominal pain (4 patients, 21%), and flatulence and steatorrhea (2 patients each, 11%).

In Table 19 below, adverse events were further categorized into which study period they occurred. The Sponsor did not have AEs recorded during the screening period (when patients were on their current PEP), thus, most AEs occurred either during the EUR-1008 dose

stabilization period or the EUR-1008 treatment period. Only a few AEs occurred after the EUR-1008 treatment period.

Table 19: Incidence Table Study 1009-M				
System Organ Class, Disorders	**Preferred Term**	**EUR-1008 Treatment Period**	**EUR-1008 Dose Stabilization Period**	**After treatment period**
		N=19(%)	**N=19(%)**	**N=19(%)**
Gastrointestinal	Abdominal pain	0	5 (26)	0
	Steatorrhea	0	3 (16)	0
	Flatulence	0	1 (5)	0
	Feces discolored	0	1(5)	0
	Abdominal distension	0	1(5)	0
	Feces discolored	1 (5)	0	0
	Steatorrhea	1 (5)	0	0
	Diarrhea	1 (5)	0	0
	Abdominal discomfort	1 (5)	0	0
	Abdominal pain	1 (5)	0	0
	Vomiting	1 (5)	0	0
	Flatulence	1 (5)	0	0
	Vomiting	0	1(5)	0
Respiratory, thoracic and mediastinal	Nasal congestion	2(11)	0	0
	Rhinorrhea	2(11)	0	0
	Cough	1(5)	0	0
	Rhinorrhea	0	1(5)	0
	Rhinorrhea	0	0	1(5)
Infections and infestations	Upper respiratory tract infection	1(5)	0	0
	Bronchitis	0	0	1(5)
	Sinusitis	0	0	1(5)
	Upper respiratory tract infection	0	0	1(5)
Metabolism and nutrition	Decreased appetite	0	1(5)	0
	Anorexia	1(5)	0	0
General disorders and administration site conditions	Pyrexia	2 (11)	0	0
	Pyrexia	0	1(5)	0
Injury, poisoning and procedural complications	Injury	0	1(5)	0
	Sunburn	0	1(5)	0
Eye	Lacrimation increased	1(5)	0	0
Nervous system	Headache	0	1(5)	0
Blood and lymphatic system	Lymphadenopathy	0	0	1(5)
Psychiatric	Insomnia	1(5)	0	0

According to Table 19, there does not appear to be much difference between AEs in the dose stabilization period and the treatment period. Due to the small study size and without the

knowledge of the AEs at Screening while patients were on their usual PEP treatment, it is difficult to draw any conclusions from this data.

5.3.2.11.6.3 Safety Summary

Exposure to EUR-1008 (with dosages of approximately 5,000 lipase units/kg/day) during the study was similar to what is currently encountered for PEP treatment in CF patients in clinical practice. There were no deaths and no AEs which led to discontinuations. One patient had an SAE of upper respiratory infection, which was felt by the investigator not to be related to study drug. There were no clinically significant abnormalities in uric acid levels (both serum and urine), and no cases of fibrosing colonopathy. AEs were reported predominantly in the GI system, with abdominal pain, flatulence and steatorrhea as the most common complaints. There were no clinically significant abnormalities in laboratory data; individual patient vital signs and physical exams remained stable throughout the study.

Therefore, treatment of very young children with EUR-1008 appeared to be well tolerated. The safety profile was consistent with that of other PEPs reported in the literature. For this application, supportive study EUR-1009-M demonstrated an acceptable safety profile for the use of EUR-1008 in CF pediatric patients ages one to six years.

5.3.2.12 Summary and Conclusions for Study EUR-1009-M

This study was designed to assess the efficacy and safety of EUR-1008 in children younger (less than age 6 years) than those studied in the pivotal study, EUR-1008-M. The results were expected to complement the data obtained in the pivotal trial, and thus, to provide a complete profile of the efficacy and safety of EUR-1008 in a broad age range for CF patients. The primary objective of the study was to compare measures of fat malabsorption for patients at Baseline (Screening visit where patient were taking their current PEP) and after treatment with EUR-1008. The primary efficacy results showed that patients had similar measures of fat malabsorption at Screening and after treatment with EUR-1008, and suggested a consistent response.

Treatment of very young children with EUR-1008 appeared to be well tolerated. There were no deaths and one SAE, which was thought to be related to underlying disease. The AEs were reported predominantly in the GI system, which is expected in this patient population and observed throughout the literature.

Overall, EUR-1008 was shown to effectively control the signs and symptoms of malabsorption and to be well tolerated in the study population. Study EUR-1009-M was supportive of the short-term efficacy and safety that was demonstrated in the pivotal study, EUR-1008-M, by extending the pediatric patient population indication for EUR-1008 treatment down to the age of one year.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The sponsor is proposing that Zentase receive the following indication:

"Zentase is indicated in patients with partial or complete exocrine pancreatic insufficiency caused by:

- Cystic fibrosis
- Chronic pancreatitis due to alcohol use or other causes
- Surgery (pancreatico-duodenectomy or Whipple's procedure, with or without Wirsung duct injection, total pancreatectomy)
- Obstruction (pancreatic and biliary duct lithiasis, pancreatic and duodenal neoplasms, ductal stenosis)
- Other pancreatic disease (hereditary, post traumatic and allograft pancreatitis, hemochromatosis Shwachman's Syndrome, lipomatosis, hyperparathyroidism)
- Poor mixing (Billroth II gastrectomy, other types of gastric bypass surgery, gastrinoma)

(b) (4) ."

Since this application is recommended to receive an Approvable action, specific wording for labeling of EUR-1008 was not negotiated during this review cycle; however, in the opinion of this Reviewer, the data submitted to the EUR-1008 application support the general statement that EUR-1008 is indicated for the treatment of steatorrhea due to EPI due to a variety of causes, including CF and CP. It is noted that all of the patients enrolled in the clinical studies submitted to the NDA had EPI due to cystic fibrosis or chronic pancreatitis.

6.1.1 Methods

The two Phase 3 clinical studies submitted to this application are reviewed in detail (see Section 5.3 for a detailed review of each of these studies), including the pivotal study EUR-1008-M and the supportive pediatric study EUR-1009-M. Each study will be discussed separately as the differences in study design do not allow for the pooling of data. Study EUR-1008-M was a randomized, double-blind, placebo-controlled, two-treatment, crossover study; and study EUR-1009-M was an open-label, multiple-dose, single-treatment study.

The primary efficacy endpoint for EUR-1008-M was to compare the coefficient of fat absorption (CFA) following oral administration of EUR-1008 and placebo or the "change in CFA". The fecal fat measurements were obtained during a 72-hour in-hospital stool collection. The pre-

specified mean change in CFA of 23% was considered to be statistically significant by the Sponsor.

As described in published consensus documents (e.g., Borowitz, DS, Grand, RJ; Durie, PR., J Pediatrics, Nov 1995), decreased CFA is an accepted indicator of EPI, and an increase in CFA is associated with enhanced pediatric growth and development. Thus, the change in CFA can be used as a reasonable marker for pancreatic enzyme activity. A clinically meaningful increase in CFA in CF patients is accepted to be an increase of 30% or greater in the most severely affected patients (i.e., those patients who have baseline CFA less than 40%). There is no accepted clinically meaningful increase in CFA that has been determined for patients with EPI due to causes other than CF; however, as EPI due to any cause has similar clinical findings, it would be reasonable to consider this degree of change as meaningful in EPI due to pancreatectomy and chronic pancreatitis. In addition, there is no accepted change in CFA that has been shown to be clinically meaningful in patients with a Baseline CFA greater than 40%. Patients with higher CFAs at baseline tend to have smaller increases in CFA with PEP administration, as these patients have a lesser capacity to respond. Therefore, and in concert with the Agency's "Guidance for Industry Exocrine Pancreatic Drug Products –Submitting NDAs", the Division accepts the use of CFA as the primary efficacy measure in the pivotal study, EUR-1008, as reasonable and appropriate.

Please see Section 5.3 for discussion of individual studies.

6.1.2 Demographics

The clinical development plan for EUR-1008 included patients ages one year to adulthood.

6.1.2.1 Pivotal Study: EUR-1008-M

There were 34 patients between the ages of 7 and 23 enrolled in EUR-1008-M (1008) with equal representation of males and females. Less than 25 percent of these patients were between the age of 7 and 11 inclusive, and almost 80 percent were 14 years of age or older. The patients were mostly homogeneous in terms of race and ethnicity, with the majority of patients being non-Hispanic and Caucasian. See Table 20 for further details.

Table 20: Demographics of EUR-1008-M

	N=34	
Age (years)	Mean (SD):	15.5 (4.6)
	Range:	8-23
Age categories	7-11:	7 (21%)
	12-13:	0
	14-17:	13 (38%)
	>17:	14 (41%)
Gender	Male:	17 (50%)
	Female:	17 (50%)
Ethnicity	Hispanic:	3 (8.8%)
	Non Hispanic:	31(91.2%)
Race	Caucasian:	32 (94.1%)
	Non-Caucasian:	2 (5.9%)
Duration (yrs) of CF	*Mean* (SD):	14 (5.5)
	Range:	3-23

6.1.2.2 Supportive Study- EUR-1009-M

There were 19 children between the ages of 1 and 6 enrolled in study 1009 with a higher percentage of males than females (63% vs.37%). Almost 50% were between the ages of 1 and 3; however, there were no patients less than 1 year of age enrolled. Once again, almost all patients were of non-Hispanic, Caucasian descent. See Table 21 for full demographic details.

Table 21: Demographics of EUR-1009-M

	N=19	
Age (years)	Mean (SD):	3.9 (1.6)
	Median:	4.2
	Range:	1-6
Age categories	<1:	0
	1-3:	9 (47%)
	4-5:	7 (37%)
	6:	3 (16%)
Gender	Male:	12 (63.2%)
	Female:	7 (36.8%)
Ethnicity	Hispanic:	2 (10.5%)
	Non Hispanic:	17 (89.5%)
Race	Caucasian:	19 (100%)
Duration (yrs) of CF	Mean (SD):	3.3 (1.5)
	Range:	1-6

6.1.3 Patient Disposition

For Study EUR-1008-M, 34 patients were enrolled, 33 patients were randomized, 32 patients completed DB treatment and comprised the efficacy analysis population, and 31 patients completed the study (the patient disposition data are represented in Table 22).

Table 22: Study 1008-M Patient Disposition

Population	**Number of Patients**
Enrolled	N=34
Randomized	N=33
Completed DB treatment	N=32
Completed study	N=31
Voluntarily withdrew consent	N=2 (one pt. before randomization; one pt. after)
Sponsor withdrew patient	N=1 (had sigmoid colectomy)
AEs causing discontinuation	N=0

In Study EUR-1009-M, all patients completed the study.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for EUR-1008-M was to compare the coefficient of fat absorption (CFA) following oral administration of EUR-1008 and placebo or the "change in CFA". The fecal fat measurements were obtained during a 72-hour in-hospital stool collection. The pre-specified mean change in CFA of 23% was considered to be statistically significant by the Sponsor.

As described in published consensus documents (e.g., Borowitz, DS, Grand, RJ; Durie, PR., J Pediatrics, Nov 1995), decreased CFA is an accepted indicator of EPI, and an increase in CFA is associated with enhanced pediatric growth and development. Thus, the change in CFA can be used as a reasonable marker for pancreatic enzyme activity. A clinically meaningful increase in CFA in CF patients is accepted to be an increase of 30% or greater in the most severely affected patients (i.e., those patients who have baseline CFA less than 40%). There is no accepted clinically meaningful increase in CFA that has been determined for patients with EPI due to causes other than CF; however, as EPI due to any cause has similar clinical findings, it would be reasonable to consider this degree of change as meaningful in EPI due to pancreatectomy and chronic pancreatitis. In addition, there is no accepted change in CFA that has been shown to be

clinically meaningful in patients with a Baseline CFA greater than 40%. Patients with higher CFAs at baseline tend to have smaller increases in CFA with PEP administration, as these patients have a lesser capacity to respond. Therefore, and in concert with the Agency's "Guidance for Industry Exocrine Pancreatic Drug Products –Submitting NDAs", the Division accepts the use of CFA as the primary efficacy measure in the pivotal study, EUR-1008, as reasonable and appropriate.

The Sponsors results show that the mean CFA for patients receiving EUR-1008 was 88% (SD= 7.9); the mean CFA for patients receiving placebo (no treatment) was 63% (SD=19.1). Therefore, the mean change in CFA was 25%. The efficacy results show a mean change in CFA that was statistically significant (p <0.001; 95% CI [-31.7, -19.3]). The FDA Statistician confirmed the results and was agreement with the Sponsor. The results are summarized in Table 23(electronically copied and reproduced from the Sponsor's submission).

Table 23: ANOVA Model Results of Coefficient of Fat Absorption (CFA, %)

	EUR-1008 (N=32)	**Placebo (N=31)**
Mean (SEM)	88.31 (1.400)	62.72 (3.432)
SD	7.920	19.108
Median	89.81	65.79
Min, Max	62.9, 98.7	28.7, 95.5
LS means (SEM)	88.28 (2.599)	62.76 (2.639)
Difference between EUR-1008 and Placebo		-25.52
95% CI		(-31.73, -19.32)
P value		<0.001

Source: EUR-1008-M Study Report (Page 63, Section 11.4.1, Table 6; Section 14, Table 14.4.1)

The results of the primary endpoint show a statistically significant mean change in CFA in patients treated with EUR-1008 as compared to patients on placebo (no treatment). The clinical significance of a mean change in CFA of 25% is challenging to interpret, and the primary endpoint results should be examined in conjunction with the changes in CFA for individual patients (Table A in Appendix), which was performed as a subgroup analysis by this Reviewer (see section 5.3.1.11.7.2 above).

Overall, the additional efficacy analysis of change in CFA by no-treatment CFA showed that the increase in CFA on EUR-1008 treatment is greatest in the most severely affected patients. For patients (n=5) with a placebo-treatment CFA <40%, the mean increase in CFA on EUR-1008 treatment was 47%, which is a clinically meaningful increase in CFA. The patients who had a higher no-treatment CFA (≥40% during placebo treatment) showed smaller increases in CFA after treatment with EUR-1008. The inverse relationship between low no-treatment CFA and change in CFA (the lower the value initially, the higher the increase) is critical to the efficacy of the study. These results support the approval of EUR-1008 for the treatment of EPI; treatment with EUR-1008 is beneficial to most patients. The treatment affect is variable; however, it

follows a trend that the greatest change in CFA is observed in the patients with the lowest no-treatment CFA.

For study EUR-1009-M, the primary efficacy endpoint was the percentage of "responders" after one and two weeks of treatment. Responders were defined as patients without steatorrhea (<30% fecal fat content) AND without symptoms of malabsorption. At screening there were 10 responders (53%), after the dose-stabilization period (Visit 3) there were 13 responders (68%), and at end of treatment there were 11 responders (58%). Please see Table I in Appendix for fecal fat values and responder status per patient and study visit.

When maintenance of response was analyzed, many patients who were screening responders continued to be responders during Visit 3 (N=9), and some patients (N=4) continued to be responders throughout the entire study. See Table 24 below.

Table 24: Responder Maintenance

Patient	Screening	Visit 3	End of Study
102901	X[1]	X	O
103901	X	X	X
104902	X	X	O
104903	X	X	X
106901	X	X	X
106904	X	X	X
110901	X	X	O
113901	X	X	O
113902	X	X	O
116902	X	O	O
101903	O[2]	X	X
102902	O	X	X
103902	O	X	X
115901	O	X	X
101902	O	O	X
101904	O	O	X
110901	O	O	X
101901	O	O	O
109902	O	O	O

[1]X= Responder
[2]O = Non-Responder

The primary efficacy results in study EUR-1009-M support the premise that patients may be successfully changed from treatment with one PEP (usual treatment) to treatment with EUR-1008 and continue to respond to therapy. Study EUR-1009-M showed that there was a persistent response to treatment with EUR-1008 for younger patients. Thus, these results can be used as supportive evidence of efficacy, and allow for the extrapolation of the efficacy results obtained in Study EUR-1008-M to a younger patient population.

6.1.5 Analysis of Secondary Endpoints(s)

For study EUR-1008-M the major secondary endpoint was the comparison of CNA after administration of EUR-1008 versus placebo. The results showed that the mean CNA for EUR-1008 and placebo were 87% and 66%, respectively. The mean change in CNA was 21.5% and this was a statistically significant change. In general, patients with the lowest placebo CNA showed the most improvement. These results are supportive of a positive enzymatic effect of PEP treatment; however, a clinically meaningful change in CNA has not been established, so the clinical relevance of these results is not known.

The other secondary endpoints in study EUR-1008-M, including the comparison of weight/BMI, serum levels of cholesterol and fat-soluble vitamins, clinical symptoms of EPI, and Quality of Life questionnaires from Screening to End of Study between the EUR-1008 and placebo treatment periods were mostly subjective or were assessed without using validated outcome measures. The relevance of these findings in a short-term study is not known, and these endpoints were not felt to be supportive of labeling.

6.1.6 Other Endpoints

There are no other endpoints evaluated that are of clinical relevance.

6.1.7 Subpopulations

Subgroup analyses by age, and gender were performed by this Reviewer, and were found not to have affected the efficacy results in study EUR-1008-M. There were too few non-Caucasian patients to perform a meaningful analysis by race. Since CF patients are mostly Caucasian, the homogeneity of race in the clinical development plan was felt to be representative of the larger US population.

Analysis of patients by placebo (no treatment) CFA subgroups showed that the patients who were the most severely affected (lowest baseline CFA) gained the most benefit of EUR-1008 treatment by having the largest increase in CFA (see section 6.1.4 Analysis of Primary Endpoint above).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All patients in the EUR-1008 clinical development program were treated according to CFF guidelines, and dosing did not exceed 2,500 U lipase/kg/meal and 10,000 U lipase/kg/day. The dose of EUR-1008 was determined on an individual basis, and patients' doses were titrated to control their symptoms of EPI while remaining within CFF guidelines.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and/or tolerance effects was not assessed in the EUR-1008 clinical development program since the clinical data obtained were from short-term studies. According to the literature, there does not appear to be the development of tolerance to PEPs and patients remain on these medications for long periods of time (typically life-long treatment).

6.1.10 Additional Efficacy Issues/Analyses

There are no other relevant efficacy analyses.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Safety data were reviewed from the three clinical studies performed in the EUR-1008 clinical development program, including EUR-1008-M, EUR-1009-M and PR-001. Study EUR-1008-M and EUR-1009-M have been described in section 5.3 (above). Study PR-001, a bioavailability study was a randomized, open-label, single-treatment, crossover study to determine the gastrointestinal bioavailability of EUR-1008 in chronic pancreatitis (CP) patients with EPI. Study PR-001 evaluated the gastrointestinal bioavailability of a fixed dose (75,000 USP lipase units) of EUR-1008 in fed adult patients with well documented CP and EPI. Safety was assessed by the review of all of the AE data.

The most important study reviewed for safety was EUR-1008-M, which was the DB, placebo-controlled study; however, all of the safety data from these three studies were reviewed in their entirety.

7.1.2 Adequacy of Data

In the opinion of this Reviewer, the Sponsor adequately categorized the adverse events using MedDRA classification.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

There was no pooling of safety data for this review. The study designs were too different to accurately evaluate pooled data, thus each study was analyzed separately.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 63 patients, ages one year to adult, received at least one dose of EUR-1008 in the EUR-1008 clinical development program. Since this application was a 505(b)(2), it was acceptable that the EUR-1008 clinical program was limited to short-term efficacy and safety studies. The long-term safety of PEPs has been established over the many years of their use. This application relied on the published medical literature for full descriptions of AE profiles.

The overall exposure to EUR-1008 was as follows:

Study EUR-1008-M
Patients exposed: 34
Mean days of exposure to EUR-1008: 30 days
Minimum, Maximum: 19, 42 days

Exposure to EUR-1008 by dose based on lipase units shows the mean dose ranged between about 3,900 U lipase to 5,700 U lipase throughout the duration of the study. Doses in each period of the study are summarized in the following table.

Table 25: Mean Doses (lipase units) by Treatment Period

Treatment Period	Open-label dose titration/stabilization period	Randomization treatment period	Open-label normalization period	Cross-over treatment period	Second open-label normalization period
Mean Doses	4,591 lipase units/kg/day	4,997 lipase units/kg/day	4,469 lipase units/kg/day	5,715 lipase units/kg/day	3,887 lipase units/kg/day

Study EUR-1009-M
Patients exposed: 19
Mean days of exposure: 19 (same for all patients)

Mean dose during dose-stabilization period: 5,094 lipase units/kg/day
Mean dose during treatment period: 5,417 lipase units/kg/day

The demographic data for studies EUR-1008-M and EUR-1009-M have been summarized and are presented in section 6.1.2 (above).

Study PR-001

Eleven patients were enrolled in study PR-001, and ten patients received a single 75,000 U lipase dose of EUR-1008 (approximately 1,000 U lipase for mean weight of 68 kg). All patients were adults with CP, who were a mean age 51 years (range 20 to 67 years). There were six males and four females exposed to EUR-1008, eight of whom were Caucasian. Mean weight was approximately 68 kg (range 51 to 103 kg).

The data in the EUR-1008 clinical development program were limited by several factors which included: small study size, use of only one pivotal study and one open-label study, a homogeneous study population, and short study duration. However, given the extensive knowledge of PEPs worldwide, the overall EUR-1008 safety program was adequate, and was consistent with the recommendations of the Guidance.

7.2.2 Explorations for Dose Response

No formal dose-response investigations were performed, but all patients were titrated to relief of symptoms, and remained within CFF guidelines. All of the dose strength tablets were used in the clinical development program.

7.2.3 Special Animal and/or In Vitro Testing

Given the extensive human exposure to PEPs, the PEP Guidance for submitting NDAs states that animal pharmacology studies with the active ingredient (pancrelipase) are not needed to support the EUR-1008 clinical development program. In addition, this was a 505(b)(2) application, thus no special animal or in vitro testing was required.

7.2.4 Routine Clinical Testing

The schedule of clinical assessments for each of the studies performed was adequate (see schedules of study visits for studies EUR-1008-M and EUR-1009-M in section 5.3), and consisted predominantly of monitoring for AEs during study drug treatment, and changes from baseline in physical examinations (including vital signs) and clinical laboratory assessments (chemistry, hematology and urinalysis). The efforts to elicit AEs were acceptable. Since PEPs are not absorbed, no ECGs were collected.

7.2.5 Metabolic, Clearance, and Interaction Workup

EUR-1008 acts locally in the GI tract to improve the absorption of lipids, fat soluble vitamins, proteins, and to a lesser extent carbohydrates; it is not systemically absorbed and absorption, distribution, metabolism, and elimination (ADME) assessments were not performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There is an extensive history of clinical use with the PEPs, and their safety profile is well described. The most serious safety concern with PEP administration is fibrosing colonopathy (FC). FC is a condition that has been reported mainly in young children with CF who are being administered delayed-release PEP formulations. Although the exact etiology of FC is not known, studies have shown that the majority of the patients in whom FC developed were taking high dose PEPs. As a result of this potential safety (and efficacy) concern, the CFF and FDA published weight-based dosing guidelines for PEP administration (see section 2.1).

The clinical development program for EUR-1008 followed the current CFF recommendations on limiting the dosages (by lipase units). No cases of fibrosing colonopathy were reported in the clinical development program; however, it is noted that cases of FC are rare, and the finding of even a single case of FC in a safety population of this size was not expected.

PEP treatment has been associated with elevated serum and urine levels of uric acid (hyperuricemia and hyperuricosuria). Uric acid levels were adequately monitored throughout the clinical studies. No clinically significant uric acid elevations were reported; however, given the short-duration of treatment and the treatment of patients who were of adequate nutritional status only, most of whom were maintained on stable doses of PEPs prior to entry into these studies, clinically meaningful changes in uric acid levels were not expected.

Despite the negative findings for FC, hyperuricemia, and hyperuricosuria in the short-term clinical development program for EUR-1008 in a small number of patients, given the concerns for these AEs with the administration of PEPs, monitoring for FC, hyperuricemia and hyperuricosuria should be addressed in any future labeling for EUR-1008, and should be a component of ongoing safety monitoring/pharmacovigilence of EUR-1008.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in the EUR-1008 clinical development program.

7.3.2 Nonfatal Serious Adverse Events

There were a total of three SAEs reported in the EUR-1008 clinical development program. In study EUR-1008-M, there were two SAEs reported by two patients, as follows:

- Patient 101805 had a lung infection for which he was admitted to the hospital and successfully treated with antibiotics.

- Patient 116801 (who had a previous history of hemoptysis) had an episode of severe hemoptysis for which he was hospitalized. No treatment was reported for the SAE, and it was recorded as resolved after 10 days.

In study EUR-1009-M, there was one reported SAE of upper respiratory tract infection. Patient 102902 was hospitalized for four days for a respiratory infection and successfully treated with antibiotics.

All of these SAEs were assessed by the investigators as likely due to underlying disease, and were not attributed to treatment with study medication.

7.3.3 Dropouts and/or Discontinuations

In study EUR-1008-M, three patients were discontinued from the study: two voluntarily withdrew consent and one patient was withdrawn by the Sponsor secondary to a protocol violation. In study EUR-1009-M, all of the patients completed the study. There were no patients in the EUR-1008 clinical development program who discontinued treatment secondary to AEs.

7.3.4 Significant Adverse Events

There were no significant AEs reported.

7.3.5 Submission Specific Primary Safety Concerns

The most serious safety concern with PEP administration is fibrosing colonopathy (submucosal fibrosis). See section 7.2.6 (above).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In study EUR-1008-M (in both treatment groups), the most frequently reported adverse events by organ systems were in the gastrointestinal (GI) and respiratory systems, as would be expected in this patient population. The most commonly reported AEs were abdominal pain (44% of patients overall), flatulence (27%), headache (24%), and abdominal distension (24%). (See section 5.3.1.11.8.2 for a complete summary of the common AEs reported in study EUR-1008-M).

In study EUR-1009-M, the gastrointestinal system had the most reported AEs, and the most commonly reported AEs were abdominal pain (reported by 26% of patients) and steatorrhea

(16%). (See section 5.3.2.11.6.2 for a complete summary of the common AEs reported in study EUR-1009-M).

In study PR-001, there were only six adverse events reported by six patients in the entire study, including sore throat, oral ulceration, thrush, elevated liver function test (mild, which normalized), elevated glucose (in a patient with diabetes mellitus), and allergic reaction (to peanuts given with jello). The investigators assessed these events as unrelated to the EUR-1008 treatment. These AEs were not unexpected given the study design and underlying disease in the patients. Given the limitations of the study design (short-term, single-dose administration) common AEs could not be assessed.

7.4.2 Laboratory Findings

Study EUR-1008-M

Blood was drawn for serum chemistry, hematology and uric acid at the: Screening visit, Day 6 of the randomization treatment period, Day 6 of the cross over treatment period, and the End of Study visit. Urinalyses, including urinary uric acid were also performed during these study visits. Clinically significant laboratory abnormalities that qualified as AEs were included in the AE datasets.

This Reviewer analyzed the laboratory values obtained per patient on each study visit. In general, all lab abnormalities were minor and did not have clinical relevance. Laboratory findings were notable for the following:

- There were three patients with minor elevations in liver enzymes, and one patient who had a clinically meaningful elevation; however, this patient was diagnosed with hepatitis and the elevation is unlikely to be related to treatment with EUR-1008.
- There were four patients with minor elevations in glucose levels.
- Three patients had minor shifts in serum uric acid levels; one patient from normal at baseline to high at end of study, and two patients from normal to low.
- There were four patients with minor elevations of lymphocytes and four patients with minor elevations of platelets.

No clinical consequences were noted from any of these findings.

Other laboratory findings (cholesterol, fat-soluble vitamins) are discussed in Section 5.3

Study EUR-1009-M

Blood was drawn for serum chemistry, hematology and uric acid at the Screening visit and End of Study visit.

Overall, there were no clinically significant trends observed for any of the laboratory parameters. Three patients experienced elevated ALT levels at the End of Study, which had been normal at Screening. These changes were minor and not clinically significant. Fluctuations in liver enzymes are common in the CF population, and these minor changes were likely due to underlying disease.

Three patients had minor shifts in serum uric acid levels: Two patients from normal at Baseline to high at End of Study, and one from normal at Baseline to low at End of Study. No clinical consequences were noted from these findings.

PR-001

Blood was drawn for serum chemistry, hematology and uric acid at the Study Day 1 and Study Day 5. This Reviewer analyzed the laboratory values obtained per patient on each study visit.

Overall, there were no clinically meaningful trends observed for any of the laboratory parameters except for glucose levels. Most of the patients had elevated glucose levels at study entry and end of study. This lab abnormality is compatible with the diagnosis of diabetes in six of the patients. In addition, one patient had markedly abnormal Screening liver enzymes with alkaline phosphatase (600), ALT (251) and AST (134). These abnormalities decreased slightly post treatment, and since they pre-dated study medication administration, were not due to study treatment. Glucose intolerance and fluctuating enzymes are also common in a chronic pancreatitis population.

7.4.3 Vital Signs

There were no clinically meaningful changes in vital signs throughout any of the three studies.

7.4.4 Electrocardiograms (ECGs)

EUR-1008 is not systemically absorbed and electrocardiogram evaluation was not part of the EUR-1008 clinical development program.

7.4.5 Special Safety Studies

There were no special safety studies performed in the EUR-1008 clinical development program.

7.4.6 Immunogenicity

EUR-1008 and other porcine-derived PEPs are not systemically absorbed, and immunogenicity testing was not performed as part of the EUR-1008 clinical development program.

7.5 Other Safety Explorations

No other safety explorations were performed. No non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

EUR-1008 and other porcine-derived PEPs are not systemically absorbed and human carcinogenicity studies were not part of the PEP clinical development program.

7.6.2 Human Reproduction and Pregnancy Data

No studies with EUR-1008 were conducted in pregnant women. It is likely that EUR-1008 will be used by pregnant women and women of reproductive potential. PEPs have likely been used over their history by pregnant women, but are not absorbed and no known effects of active ingredients on pregnant women or their offspring are known.
Future labeling should address safety in pregnancy.

7.6.3 Pediatrics and Effect on Growth

PEPs are widely recognized as having a positive effect on growth in pediatric patients with CF.[4,5] Studies performed in the EUR-1008 clinical development program were, for the most part, short-term studies where long-term growth and development were not assessed, which is consistent

[4] Borowitz, DS; Grand, RJ; Durie, PR; Consensus Committee (sup A). Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. J Pediatrics.127(5), Nov 1995, pp 681-684. (PMID: 7472816)
[5] Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol. 2006;20(3):531-46. (PMID: 1470282)

with the recommendations for study designs in the Guidance for submitting PEP NDAs. Thus, no formal assessments of pediatric growth and development were performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

PEPs are not systemically absorbed and there is no potential for abuse, withdrawal, or rebound.

An important safety issue regarding PEP use and the potential for overdose is fibrosing colonopathy (FC). The etiology of FC has not been definitively established, but is thought to be associated with high dose lipase exposure, although some reports indicate the risk of FC is associated with the excipients.[4, 5] In order to optimize therapy while minimizing the risk of FC, the Cystic Fibrosis Foundation (CFF) in conjunction with the FDA recommends starting lipase doses according to age as described below.

The CFF recommends the following dose schedule for full meals:

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.
- Children <4 years old eating soft or solid foods: begin with 1,000 USP lipase units/kg/meal.
- Children >4 years old: begin with 500 lipase units/kg/meal.
- Doses in excess of 2,500 USP lipase units/kg/meal should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to significantly improve a documented low coefficient of fat absorption.
- The recommended per meal dose should be halved when ingesting snacks.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with fibrosing colonopathy.

Recommendations for snacks are half the dose taken at meals. Daily doses are not to exceed 10,000 U lipase/kg/day (3 meals, 2 snacks).

These recommendations should be included in product labeling for EUR-1008 and for all PEPs.

7.7 Additional Submissions

A 120-Day Safety Update Report was submitted by the Sponsor on May 20, 2008. Pertinent finding from the report are presented below:

Complete safety data and final study reports for the administration of EUR-1008 to patients in the two Phase 3 clinical studies (EUR-1008-M and EUR-1009-M) were reported in the NDA. No extension study was done for either of these two Phase 3 studies. The EUR-1008 NDA also

included complete safety and performance data from the first eight patients treated in the Gastric Bioavailability Study (PR-001). Enrollment in this study is ongoing.

The Safety Update Report covered the period from December 14, 2007 through March 30, 2008. During this period, the sponsor had two active clinical studies (PR-001 and PR-002). These two studies constitute the full worldwide human exposure of EUR-1008 during this reporting period. Safety data from two new patients in study PR-001, who have completed the protocol and whose data are considered final, show no AEs or SAEs. For the study PR-002, no patient data were available as of the March 30, 2008 closing date for the Safety Update. For both studies listed above, no deaths, discontinuations or withdrawals, for any reason, occurred during the reporting period of this Safety Update Report.

Thus, there were no new or additional safety findings reported in the 120-day Safety Update.

8 Postmarketing Experience

EUR-1008 is not a marketed product so there is no postmatketing experience available; however, the active ingredient in EUR-1008, pancrelipase, is presently widely available from several different manufacturers as enteric coated (EC) and non-EC formulations (which are not interchangeable). Thus, many different PEP formulations are currently available in the United States and worldwide. Overall, the safety information reported in the EUR-1008 clinical development program is consistent with the safety profile of PEPs reported in the published literature, and no additional safety information from this worldwide experience, other than as noted in this review (e.g., FC, hyperuricemia, and hyperuricosuria), is to be included in product labeling.

9 Appendices

9.1 Literature Review/References

Please see individual references noted throughout this review.

9.2 Labeling Recommendations

Since this NDA is recommended to receive an Approvable action, the labeling was not negotiated with the Sponsor during this review cycle. However, should EUR-1008 be approved during a future review cycle recommendations for future labeling include:

- Recommended indication: EUR-1008 is indicated for the treatment of steatorrhea due to EPI due to a variety of causes, including CF and CP, for patients ages one year to adult.

- Viral issues: Since PEPs are derived from pig pancreata, there is a theoretical and potential risk of transferring certain species-specific viruses to patients taking PEPs (e.g., porcine parvovirus). Thus, labeling should note that live virus are present in the capsule, and that potential risk of transmission exists, although no human transmission due to PEP exposure has been reported to date.

- Clinical Studies EUR-1008-M (pivotal study) and EUR-1009-M (as supportive study) should be included in the labeling, and it should be noted that all of the patients treated with EUR-1008 have had EPI secondary to CF or CP.

- Pediatric limitations: Only patients one year of age or older were included in clinical studies.

- Dosage recommendations: To follow CFF recommendations; see Section 7.5.4 .

- Warnings: Cases of fibrosing colonopathy has been reported in young CF patients on high doses of PEPs. There have been reports of elevated serum and urine uric acid levels in patients taking PEPs.

- Dosing instructions: do not open microtabs to estimate doses.

- Secondary endpoints: not to be included in labeling.

9.3 Advisory Committee Meeting

No Advisory Committee was convened for this application.

9.4 Additional Tables

9.4.1 Study EUR-1008-M: CFA Results by Individual Patient

Table A: Study EUR-1008-M, CFA Results by Individual Patient

Patient Number	Placebo CFA	EUR-1008 CFA	Change in CFA
103804	(b) (4)		
112803			
102802			
108801			
105801			
101804			
103802			
109806			
103801			
116802			
105805			
105804			
118803			
109803			
109805			
105807			
112805			
101802			
105806			
115803			
103803			
118802			
112804			
115801			
105803			
106801			
101805			
109804			
115802			
112801			
108802			
116801			

9.4.2 Study EUR-1008-M: CFA Results, Males

Table B: Study EUR-1008-M, Results for Males

Patient number	Placebo	Zentase	Change in CFA
101805	(b) (4)		
102802			
103801			
103804			
105804			
105805			
105806			
105807			
108802			
109803			
109804			
112803			
116801			
116802			
118802			
118803			

9.4.3 Study EUR-1008-M: CFA Results, Females

Table C: Study EUR-1008-M, Results for Females

Patient number	Placebo CFA	Zentase CFA	change in CFA
101802	(b) (4)		
101804			
103802			
103803			
105801			
105803			
106801			
108801			
109805			
109806			
112801			
112804			
112805			
115801			
115802			
115803			

9.4.4 Study EUR-1008-M: CFA Results, Patients Aged 7 to 11 Years

Table D: Change in CFA for Patients Aged 7 to 11 Years

Patient	Placebo	EUR-1008	Change in CFA	Age
102802	(b) (4)			
105801				
116802				
118803				
109805				
103803				
118802				
109804				
Mean	**61**	**83**	**22**	**9**
Median	**63**	**85**	**21**	**8.6**
Min, Max	(b) (4)			

9.4.5 Study EUR-1008-M: CFA Results, Patients Aged 12 to 16 Years

Table E: Change in CFA for Patients Aged Patients Ages 12-16

Patient	Placebo	EUR-1008	Change in CFA	Age
112803	(b) (4)			
103802				
103801				
105805				
105804				
109803				
105807				
101802				
112804				
115801				
105803				
106801				
108802				
Mean	**64**	**89**	**28**	**15.2**
Median	**66**	**89**	**22**	**14.8**
Min, Max	(b) (4)			

9.4.6 Study EUR-1008-M: CFA Results, Patients Aged ≥ 17 Years

Table F: Change in CFA for Patients Aged Patients ≥ 17

Patient	Placebo	EUR-1008	Change in CFA	Age
103804	(b) (4)			
108801				
101804				
109806				
112805				
105806				
115803				
101805				
115802				
112801				
116801				
Mean	**66**	**91**	**25**	**21**
Median	**69**	**93**	**26**	**21**
Min, Max	(b) (4)			

9.4.7 Study EUR-1008-M: CNA Results

Table G: CNA Values

Patient	**Placebo N=32**	**EUR-1008 N=32**	**Change in CNA**
108802		(b) (4)	
112803			
102802			
116802			
105801			
118803			
103804			
108801			
118802			
103802			
105805			
101804			
109806			
103801			
109805			
109803			
105807			
106801			
112804			
112805			
105803			
115803			
103803			
105806			
101802			
115801			
101805			
109804			
105804			
116801			
115802			
112801			
Mean	**66**	**87**	**21**
Median	**70**	**88**	**23**
Min, Max		(b) (4)	

9.4.8 Study EUR-1008-M: All Adverse Events

Table H: Study EUR-1008-M, AE Incidence Table, All AEs

		All	EUR-1008	Placebo
		N=34 (%)	N=34 (%)	N=32 (%)
System Organ Class, Disorders	**Preferred Term**			
Gastrointestinal	Abdominal pain	15 (44)	9 (26)	6 (19)
	Flatulence	9 (26)	6 (18)	3 (9)
	Abdominal distension	8 (24)	5 (15)	3 (9)
	Steatorrhea	6 (18)	2 (6)	4 (13)
	Abdominal pain upper	5 (15)	2 (6)	3 (9)
	Abnormal feces	5 (15)	2 (6)	3 (9)
	Frequent bowel movements	4 (12)	2 (6)	2 (6)
	Nausea	3 (9)	2 (6)	1 (3)
	Abdominal discomfort	2 (6)	2 (6)	0
	Dyspepsia	2 (6)	2 (6)	0
	Vomiting	2 (6)	2 (6)	0
	Abdominal tenderness	1 (3)	1 (3)	0
	Bowel sounds abnormal	1 (3)	0	1 (3)
	Constipation	1 (3)	1 (3)	0
	Dry mouth	1 (3)	1 (3)	0
	Infrequent bowel movements	1 (3)	0	1 (3)
General and administration site conditions	Early satiety	2 (6)	2 (6)	0
	Pyrexia	2 (6)	2 (6)	0
	Chest pain	1 (3)	1 (3)	0
	Edema mucosal	1 (3)	1 (3)	0
Hepatobiliary	Hepatitis	1 (3)	1 (3)	0
Infections and infestations	Otitis externa	1 (3)	0	1 (3)
	Pertussis	1 (3)	1 (3)	0
Injury, poisoning and procedural complications	Contusion	2 (6)	2 (6)	0
	Injury	2 (6)	2 (6)	0
	Anal injury	1 (3)	1 (3)	0
	Arthropod bite	1 (3)	1 (3)	0
	Fall	1 (3)	0	1 (3)
	Medical device complication	1 (3)	1 (3)	0
Investigations	Weight decreased	4 (12)	2 (6)	2 (6)
	Pulmonary function test decreased	2 (6)	2 (6)	0
	Blood potassium decreased	1 (3)	1 (3)	0
	Liver palpable subcostal	1 (3)	1 (3)	0
Metabolism and nutrition	Anorexia	1 (3)	0	1(3)
Musculoskeletal and connective tissue	Arthralgia	1 (3)	1 (3)	0
	Clubbing	1 (3)	1 (3)	0
	Myalgia	1 (3)	1 (3)	0
	Pain in extremity	1 (3)	1 (3)	0

Table H: Study EUR-1008-M, AE Incidence Table, All AEs

		All	EUR-1008	Placebo
		N=34 (%)	N=34 (%)	N=32 (%)
System Organ Class, Disorders	**Preferred Term**			
Nervous system	Headache	8 (24)	8 (24)	0
	Dizziness	2 (6)	1 (3)	1 (3)
Reproductive system and breast	Dysmenorrhea	1 (3)	1 (3)	0
	Vaginal burning sensation	1 (3)	0	1 (3)
Respiratory, thoracic and mediastinal	Cough	4 (12)	4 (12)	0
	Crackles lung	2 (6)	1 (3)	1 (3)
	Nasal congestion	2 (6)	2 (6)	0
	Dysphonia	1 (3)	1 (3)	0
	Hemoptysis	1 (3)	1 (3)	0
	Lung disorder	1 (3)	1 (3)	0
	Productive cough	1 (3)	1 (3)	0
	Rhinorrhea	1 (3)	1 (3)	0
Skin and subcutaneous tissue	Blister	1 (3)	1 (3)	0
	Pruritus	1 (3)	1 (3)	0
	Rash	1 (3)	1 (3)	0
Vascular	Hematoma	1 (3)	1 (3)	0

9.4.9 Study EUR-1009-M: Fecal Fat Results/Responders by Study Visit

Table I: Fecal Fat Values/Responders by Study Visit

Patient	Visit	Responder 1 = yes, 0 = no	Baseline (Screening) Fecal Fat %	Fecal Fat %	Change Fecal Fat %
101901	SCREENING	0		(b) (4)	
101901	VISIT 3	0			
101901	END OF STUDY	0			
101902	SCREENING	0			
101902	VISIT 3	0			
101902	END OF STUDY	1			
101903	SCREENING	0			
101903	VISIT 3	1			
101903	END OF STUDY	1			
101904	SCREENING	0			
101904	VISIT 3	0			
101904	END OF STUDY	1			
102901	SCREENING	1			
102901	VISIT 3	1			
102901	END OF STUDY	0			
102902	SCREENING	0			
102902	VISIT 3	1			
102902	END OF STUDY	1			
103901	SCREENING	1			
103901	VISIT 3	1			
103901	END OF STUDY	1			
103902	SCREENING	0			
103902	VISIT 3	1			
103902	END OF STUDY	1			
104902	SCREENING	1			
104902	VISIT 3*	1			
104903	SCREENING	1			
104903	VISIT 3	1			
104903	END OF STUDY	1			
106901	SCREENING	1			
106901	VISIT 3	1			
106901	END OF STUDY	1			
106904	SCREENING	1			
106904	VISIT 3	1			
106904	END OF STUDY	1			
109902	SCREENING	0			
109902	VISIT 3	0			
109902	END OF STUDY	0			
110901	SCREENING	1			
110901	VISIT 3	1			
110901	END OF STUDY	1			
113901	SCREENING	1			
113901	VISIT 3	1			
113901	END OF STUDY	0			
113902	SCREENING	1			

Patient	Visit	Responder 1 = yes, 0 = no	Baseline (Screening) Fecal Fat %	Fecal Fat %	Change Fecal Fat %
113902	VISIT 3	1		(b) (4)	
113902	END OF STUDY	0			
115901	SCREENING	0			
115901	VISIT 3	1			
115901	END OF STUDY	1			
116901	SCREENING	0			
116901	VISIT 3	0			
116901	END OF STUDY	0			
116902	SCREENING	1			
116902	VISIT 3	0			
116902	END OF STUDY	0			

* Patient 104902 had no end of study value

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/s/

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