

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-210

MEDICAL REVIEW(S)

Medical Officer's Review of Safety Update Report

NDA#: 22, 210

Sponsor: Eurand Pharmaceuticals Inc.

Product: Zenpep

Therapeutic Class: Pancreatic Enzyme Product (PEP)

Indication: Treatment of exocrine pancreatic insufficiency (EPI)

Date Submitted: June 12, 2009

Date Received: June 12, 2009

PDUFA Date: June 23, 2009

Extended PDUFA Date: September 23, 2009

Date of Review: August 12, 2009

Clinical Reviewer: Marjorie F. Dannis, M.D., Medical Officer, DGP

Through: Anil Rajpal, M.D., Acting Team Leader, DGP

Regulatory Update

During the initial review cycle for NDA 22, 210, PDUFA goal date of June 17, 2008, Eurand Pharmaceuticals Inc. stated that its pancrelipase product, EUR-1008 (Zenpep), had "never been marketed", thus no additional safety information was available except the data from three clinical trials which were submitted to the original NDA. A 120-Day Safety Update was submitted during the later part of the first review cycle (May 20, 2008) and covered the period from December 14, 2007 through March 30, 2008. In the 120-Day Safety Update, the Sponsor stated that complete safety data for the administration of Zenpep 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. NDA 22, 210 also included complete safety and performance data from the first eight patients treated in the Gastric Bioavailability Study (PR-001).

During this reporting period, the sponsor had two active clinical studies (PR-001 and PR-002). According to the Sponsor, "these two studies constituted the full worldwide human exposure of EUR-1008 during this reporting period." Safety data from two new patients in study PR-001, who had completed the protocol and whose data were considered final, showed 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.

During the second cycle review for NDA 22, 210, PDUFA goal date June 23, 2009, new clinical information became available to the Division. In the "Response to FDA Information Request Letter dated April 23, 2009," Eurand responded with the following statement:

"We would like to reiterate that Eurand provides unbranded pancrelipase product to the marketplace in association with IND 70,563 and NDA 22-210".

Since Eurand was continuing to market a pancrelipase product "in association with IND 70,563 and NDA 22-210," complete safety information was required to be submitted to the Division in association with either IND 70,563 or NDA 22-210. No safety information for Eurand's unbranded pancrelipase product was provided in the original NDA submission or subsequent Safety Updates.

On June 12, 2009, the Sponsor submitted a limited comprehensive safety summary. This late submission of required safety data for the unbranded pancrelipase product constituted a major amendment, thus the PDUFA clock was extended by three months to a new goal date of September 23, 2009.

Safety Update

A Safety Update Report was submitted by the Sponsor on June 12, 2009. This report covered the period from January 1, 1999 through June 1, 2009; this was the only safety report that had been submitted for the unbranded pancrelipase product. Pertinent findings from the report are presented below.

Adverse Events

Overall, 15 case reports of adverse events were received; two of these reports were serious spontaneous reports (one hospitalization and one pancreatic growth), while 13 of the case reports were non-serious (predominantly gastrointestinal signs and symptoms and/or lack of efficacy) spontaneous reports. The most frequently reported adverse events were lack of efficacy (8), followed by diarrhea (4) and flatulence (2). The remaining cited

adverse events were single occurrences. See Tables 1 and 2 below (electronically scanned and reproduced from Sponsor's submission).

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Table 1. Adverse Events by Listings for the unbranded pancrelipase product

Gastrointestinal Disorders	7 Reports	Diarrhea 4 Flatulence 2 Bloating 1 Vomiting 1 Worsening of GI symptoms 1 RUQ pain 1 Steatorrhea 1
Lack of Efficacy	8 Reports	Lack of Efficacy 8
General Administration Disorders, Other	1 Report	Rash 1 Polyps 1 Pancreatic growth 1
Body as Whole, NOS	2 Reports	Chest pain 1 Does not feel well 1
Cardiovascular	1 Report	Hypotension 1

Table 2. Summary of the total safety experience from January 1, 1999 to June 1, 2009

Date Impax Received	Eurand Medwatch File #	Product	Report Source	Serious & Fatal Cases	Non Serious Cases	Brief description		Outcome or Resolution
1/17/03	PAN200301	Lipram UL-20	HCP		X	Gastrointestinal Disorders	Eurand complaint 0129 Impax CO3-002 Increased gas, diarrhea Medwatch File No 03-000651	Unknown
3/21/03	PAN200302	Lipram CR-20	Consumer		X	Gastrointestinal Disorders	Impax #CO3-009 Bloating and Flatulence ineffective	Unknown
4/10/03	PAN200303	Lipram UL-20	Consumer		X	Gastrointestinal Disorders	Impax # CO3-012 vomiting, diarrhea	Unknown
6/13/03	PAN200305	Lipram	Consumer		X	LOE	Impax complaint # CO3-018 LOE	Unknown
8/11/03	PAN200304	Lipram PN-10	HCP to Impax	X		General Administration Disorders, Other	Eurand complaint #0136, Impax # CO3-025: Rash, raised bumps and skin became red and burst; polyps in nose & pancreatic growth	Unknown
6/13/03	PAN200306	Lipram 4500	Consumer to Impax		X	Body as whole, NOS	Impax complaint number CO3-019. Patient complaint of chest pain	Chest pain due to chest cold. Both pats PCP and ER MD told him to continue taking Lipram
6/20/03	PAN200307	Lipram PN16	HCP to Impax		X	Body as whole, NOS	Impax complaint # CO3-022 Patient did not feel well after taking the medication	Unknown
7/18/03	PAN200308	Pancrelipase tablets 8000	Consumer to Impax		X	Gastrointestinal Disorders	Impax complaint number CO3-020 Diarrhea and drop in BP	Unknown
3/21/05	PAN200501	Orbexa 10,000	Consumer to Impax		X	LOE	Eurand complaint 0157; Impax CO5-021: LOE Medco sent in Medwatch Medwatch File #-0501516	Unknown
11/02/05	PAN200502	Lipram 4500	HCP to Impax		X	LOE	Impax Complaint # CO5-088 Patient complains that drug is ineffective	Symptoms Resolved - "patient feels better"
1/5/06	PAN200601	PN-20	Consumer to Impax		X	Gastrointestinal Disorders	Eurand complaint #0160; Impax; complaint # CO6-003 Patient experienced diarrhea and pain	Unknown
1/06/06	PAN200602	LipramUL-18	Consumer to Impax		X	Gastrointestinal Disorders LOE	Eurand complaint #0161; Impax # CO6-004 Patient stated that the product had no effect. Test results showed fat present in	Unknown

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Table 2 (continued). Summary of the total safety experience from January 1, 1999 to June 1, 2009 (continued)

Date Impax Received	Eurand Medwatch File #	Product	Report Source	Serious & Fatal Cases	Non Serious Cases	Brief description		Outcome or Resolution
							feces	
10/10/2006	PAN200604	Lipram 4500	Consumer to Impax		X	LOE	Impax complaint # CO6-0357 Lack of Efficacy	Unknown
11/02/06	PAN200603	Lipram 4500	HCP to Impax		X	LOE	Eurand complaint #0184; Patient complains that drug is ineffective	Unknown
3/26/07	PAN200701	Orbexa Lipram 4500	Consumer to Impax	X		Gastrointestinal Disorders LOE	Eurand complaint #0187; Impax CO7-0108; LOE, Worsening of Symptoms/ RUQ abdominal pain, hospitalization, MEDCO sent in Medwatch Medwatch file number 07-01317	Patient discharged from hospital Symptoms resolved with new prescription

The limited adverse event data presented above are consistent with the known adverse event profile of pancreatic enzyme products (PEPs).

Cumulative sales and exposure of the unbranded pancrelipase product

The total US sales of the unbranded pancrelipase product during the reporting period was (b) (4) capsules. This number is the entire bulk finished product which was manufactured by Eurand. Table 3 below (electronically scanned and reproduced from Sponsor's submission) represents the total sales of each dosage strength.

Table 3. Summary of the total US sales of capsules

No of capsules	Dosage form, Product, and Strength
(b) (4)	capsules of 4,500 units
	capsules of 5,000 units
	capsules of 10,000 units
	capsules of 12,000 units
	capsules of 16,000 units
	capsules of 18,000 units
	capsules of 20,000 units

Table 4 below (electronically scanned and reproduced from Sponsor's submission) provides a summary of the estimated total patient exposure per calendar year per strength. The estimate for patient exposure is calculated from the number of capsules sold and the average daily dose, assuming an average daily dose of 15 capsules for patients with cystic fibrosis. Thus, during the reporting period, patient exposure to the unbranded pancrelipase product was estimated to be between (b) (4) "patient treatment-months".

In addition, the Sponsor reported that there were no preclinical or clinical studies conducted with the unbranded pancrelipase product during the reporting period.

Summary/Conclusion

The limited safety information submitted in the Safety Update Report covering the period of January 1, 1999 through June 1, 2009 appears to be consistent with the known adverse event profile of PEPs. The total US sales of the unbranded pancrelipase product during the reporting period was [REDACTED] (b) (4) capsules. Patient exposure to the unbranded pancrelipase product was estimated to be between [REDACTED] (b) (4) “patient treatment-months”.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22210	----- ORIG 1	-----	----- ZENTASE

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/s/

MARJORIE F DANNIS
08/12/2009

ANIL K RAJPAL
08/12/2009

Memorandum

RE: EUR-1008 (pancrelipase delayed-release capsules) for Exocrine Pancreatic Insufficiency

Date: June 16th, 2008

From: Daniel A. Shames MD FACS
Deputy Director, Office of Drug Evaluation III
CDER/FDA

To: File (DFS)

NDA #: 22-210
Applicant: Eurand Pharmaceuticals, Inc.
Proposed Trade Names: Zentase, ZenPep, Zenase (trade name to be determined)
PDUFA goal date: June 17, 2008
Formulation: EUR-1008 capsules 5000,10,000,15,000,20,000 units (U)
lipase for oral administration,
Proposed indication: Treatment of exocrine pancreatic insufficiency (EPI)
Proposed regimen: Up to 2,500 lipase units per kg per meal, not to exceed
10,000 lipase units per kg per day

Recommended Regulatory Action: Approvable (AE) because of CMC and Clin Pharm deficiencies.

Attribution: I primarily consulted the reviews of the Cross Discipline Team Leader, Ann Pariser MD and the Medical Reviewer, Marjorie Dannis MD for the creation of this Memorandum.

1.0 Background (General)

1.1 Pancreatic Enzymes

1.11 Clinical

Exocrine pancreatic insufficiency (EPI) typically results from chronic loss of pancreatic tissue due a number of underlying diseases and conditions. Cystic Fibrosis (CF) is the most common cause of EPI in children, and chronic pancreatitis (CP) due to alcoholism or idiopathic pancreatitis is the most common cause of EPI in adults; however, there are a large number of other causes, such as pancreatectomy. Clinical manifestations of EPI are predominantly steatorrhea, abdominal pain, weight loss, and nutritional problems (e.g., fat-soluble vitamin deficiencies) due to malabsorption. The main stay of therapy for steatorrhea and malabsorption due to EPI, regardless of cause, has been the administration of pancreatic enzyme replacement therapy (PERT) with exogenous sources of pancreatic enzyme product (PEP).

1.12 Product

The drug substance (DS) is derived from porcine pancreas glands harvested from pigs raised as human food. The glands are obtained from slaughter houses, are deep-frozen, and remain frozen until they are processed by the manufacturer. The glands then undergo (b) (4) resulting in the pancrelipase DS to be used for manufacture of drug

product (DP). Characterization of the enzymes contained in the DS, including assays for amylase, lipase, protease (total and a number of individual proteases, such as (b) (4) are performed.

1.13 Regulatory

PEPs are currently widely available in the United States (US) as non-prescription nutritional supplements or over-the-counter (OTC) medications, or by prescription. PEPs are available as enteric-coated/delayed-release and non-enteric coated formulations. These formulations are not considered to be interchangeable.

PEPs have been available in the US since prior to the Federal Food, Drug, and Cosmetic Act (The Act) of 1938. Most PEPs have been available since pre-Drug Efficacy Study Implementation (DESI; pre-1962), and have never undergone formal evaluation under Investigational New Drug (IND) applications or NDAs for efficacy or safety. Substantial variations among currently marketed products exist, including variations in formulation, dosage, and manufacturing processes, both between the different PEPs and within the individual PEP brands (from lot to lot and even within lots). Variations in drug potency that result from this product variability are known to exist, and may significantly affect the safety and effectiveness of the PEPs.

To address the problems with variations between the PEPs, the Food and Drug Administration (the Agency) published the following notices in the Federal Register (FR):

- In 1979, the Agency proposed establishing monographs for OTC PEPs.
- In 1985, recommendations of the PEP Advisory Review Panel were published that stated that OTC monographs would not be sufficient to regulate the PEPs, preclearance of each product to standardize enzyme bioactivity would be necessary, and PEPs should be made available by prescription only.
- In 1991, the Expert panel proposed that the FDA withdraw the 1985 proposed OTC rule, declared that the PEPs are not Generally Recognized as Safe (GRAS) and Generally Recognized as Effective (GRAE), and the PEPs are misbranded.
- In 1995, a Notice of Final Rule was published that stated all PEPs must obtain FDA approval (under NDA) in order to remain on the market.
- In 2004, the Notice of Requirement for NDA Approval was published that stated all PEPs must get NDA approval within the next four years (deadline 28-April-2008), and the expectation of the Agency was that only NDAs under 505(b)(2), not Abbreviated New Drug Applications (ANDAs), would be received. To be approved, PEP NDAs must meet the requirements for content and format of an application as stated in 21CFR 314.50. A draft Guidance for submitting NDAs for PEPs was also published at that time.¹

¹ 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." 2004.

- In 2006, the Final Guidance for submitting NDAs for PEPs was published (heretofore referred to as “the Guidance”).²

Note: These FR notices and the Guidance only apply to the currently-marketed, animal (porcine or bovine)-derived PEPs containing pancreatin and pancrelipase.

Currently, there is only one approved NDA for a PEP: Cotazyme, an immediate-release PEP (NDA 20-580); however, Cotazym is not currently marketed in the US. Thus, no approved PEPs are currently commercially available in the US under NDA

2.0 NDA 22-210 (EUR-1008)

2.1 Regulatory

This submission is the initial New Drug Application (NDA) submission for EUR-1008. EUR-1008 is a New Molecular Entity (NME) that was granted priority review. This NDA submission was received on 17-December-2007, and the Prescription Drug User Fee Act (PDUFA) goal date is 17-June-2008.

2.2 Clinical

While there is no previous clinical experience with the current formulation EUR-1008, there is considerable clinical experience with similar formulations of porcine-derived PEPs manufactured by Eurand (Ultrase® marketed by Axcan Pharma, and Lipram® by Global Pharmaceuticals) and by other manufacturers.

The NDA submission contains efficacy and safety information from two studies (EUR-1008M, EUR-1009M). Because EUR-1008M was a placebo controlled, randomized study and the larger of the two studies, it was the most valuable in terms of evaluating the overall efficacy and safety of EUR-1008.

2.21 Efficacy Analysis and Conclusion

2.211 EUR-1008M

Study EUR-1008M was a multi-center, randomized, double-blind (DB), placebo-controlled, two-treatment, cross-over study of EUR-1008 administered to 34 patients with CF and EPI, ages 8 to 23 years. The objectives of the study were to describe the short-term (approximately 20 to 35 days) efficacy and safety of EUR-1008. Efficacy was assessed by the difference in a 72-hour fecal fat collection analysis of EUR-1008 as compared to placebo.

The primary efficacy endpoint was the comparison of percent coefficient of fat absorption (%CFA). %CFA is determined from a 72-hour stool collection (usually while the patient is consuming a high-fat diet) and is calculated as follows:

$$\%CFA = \frac{[\text{Fat intake (g/day)} - \text{Fat excretion (g/day)}]}{\text{Fat intake (g/day)}} \times 100$$

² 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.htm>> April 2006. Shames/AE/22-210

A change in %CFA of 30% or greater in severely affected patients (patients with a no-treatment %CFA of 40% or less) is considered to be clinically meaningful, but no accepted change in %CFA has been established for patients with no-treatment %CFA greater than 40%. However, change in %CFA with active treatment is expected to be larger in more severely affected patients, as the more severely affected patients have a greater capacity to respond to treatment. Thus, the results of the studies are expected to be at least partly dependent on the severity of patients disease (by no-treatment %CFA at Baseline) enrolled in the studies.

The analysis of the primary efficacy endpoint data for EUR-1008M showed that the mean CFA for patients during placebo treatment was 63%, and during EUR-1008 treatment was 88%. The mean difference in CFA on EUR-1008 as compared to placebo was 25%, which was a statistically significant difference ($p < 0.001$; 95% CI [-32, -19]). The results are summarized in the following table (electronically copied and reproduced from the sponsor's submission).

Table 1: ANOVA Model Results of Coefficient of Fat Absorption (CFA; %)

	EUR-1008 (N=32)	Placebo (N=31)
Mean (SEM)	88.3 (1.4)	62.7 (3.4)
SD	7.9	19.1
Median	89.8	65.8
Min, Max	62.9, 98.7	28.7, 95.5
LS means (SEM)	88.3 (2.6)	62.8 (2.66)
Difference between EUR-1008 and Placebo		-25.5
95% CI		(-31.7, -19.3)
<i>P</i> value		<0.001

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

A subgroup analysis by no-treatment % CFA at baseline was performed. This analysis showed that for the severely-affected patients (CFA \leq 40%, n=5) the mean CFA during placebo treatment was 35%, mean CFA during EUR-1008 treatment was 82%, and the mean difference of EUR-1008 as compared to placebo was 47%. This difference between the two treatment periods is clinically meaningful. For the moderately-affected patients (CFA 40% to 80%, n=21), the mean CFA during placebo treatment was 62%, mean CFA during EUR-1008 treatment was 88%, and the mean difference on EUR-1008 as compared to placebo was 26%. For the mildly-affected patients (CFA \geq 80%, n=5), the mean CFA during placebo treatment was 93%, mean CFA during EUR-1008 treatment was 94%, and the mean difference on EUR-1008 as compared to placebo was 1%.

The results overall show that treatment effect tends to have a linear relationship with the baseline (no-treatment) condition of the patient for the primary endpoint. That is, patients who were more severely affected (lower no-treatment CFA), tended to have higher increases in CFA on EUR-1008. This result is consistent with the previous experience with the PEPs, since patients with a lower CFA on no-treatment have a higher capacity to respond to treatment. No other factors were identified in this study that appeared to have an effect on response, including treatment sequence, age, or gender.

2.212 EUR-1009 (Pediatric Study)

Study EUR-1009 was a multi-center, non-randomized, open-label, uncontrolled, single-arm, short-term (eight-week), safety and efficacy study of EUR-1008 in 19 children with CF and EPI, ages one to six years. The objectives of the study were to compare measures of fat malabsorption (by spot fecal fat testing) while on EUR-1008 or their usual PEP treatment. Per Cystic Fibrosis Foundation recommendations that young children not undergo wash-out, placebo, or no-treatment periods, all patients were maintained on either their usual PEP treatment or on EUR-1008 throughout the duration of the study.

The primary endpoint was spot fecal fat testing with each bowel movement over a three-day period, since 72-hour stool collections, which are required for CFA, are difficult to obtain in young children. Spot fecal fat testing is not considered as a measure of definitive evidence of effectiveness; however, spot testing is believed to be acceptable in this patient population for providing evidence of responsiveness (fecal fat content <30%), which could allow for extrapolation of the CFA results from older children and adults.

The primary endpoint analysis was the percentage of “responders” after one and two weeks of treatment with EUR-1008. Responders were defined as patients without steatorrhea (<30% fecal fat content) *and* without signs and symptoms of malabsorption (e.g., normal stool consistency) at Days 11 and 18 (after 7 and 14 days, respectively, of EUR-1008 treatment) compared with Screening (while on usual PEP treatment).

The primary efficacy endpoint analysis showed that the percentage of “responders” at Screening (on usual treatment) was ten patients (53%), at Visit 3 (at the end of the Dose-Stabilization Period) was 13 patients (68%), and at the End-of-Study visit (at the end of the Treatment Period) was 11 patients (58%). Four patients (21%) were classified as responders at each visit during the study, and two patients were non-responders at all visits during the study. For the ten patients who were classified as responders at Screening, nine of these patients were classified as responders during at least one of the two study visits after transition to EUR-1008 treatment. For the nine patients who were non-responders at Screening (on usual treatment), seven of these patients were classified as responders at Visit 3 or the End-of-Study visit (or both) while on EUR-1008 treatment.

The Medical Reviewer additionally analyzed the results of the fecal fat testing alone, without the subjective assessment of response by signs and symptoms of malabsorption. The results show that for the cut-point of fecal fat <30% selected by the Applicant as defining patients without steatorrhea, at Screening 14 of 19 patients had a fecal fat <30%, at Visit 3 13 of 19 patients had a fecal fat <30%, and at End-of-Study 13 of 18 patients had a fecal fat <30%, and throughout the study, 16 of 19 patients had a fecal fat <30% at one or more study visits. Thus, the majority of patients were without steatorrhea during the study, whether on their usual PEP treatment or after transition to treatment with EUR-1008.

Overall, these results are consistent with most patients in the study showing response to PEP treatment whether on their usual treatment at Screening or after transition to EUR-1008. Thus, these results are supportive of the effectiveness of EUR-1008 in pediatric patients with CF and EPI, ages one to six years of age. The results would allow for the extrapolation of the benefit of treatment seen with EUR-1008 (by change in CFA) obtained in the Pivotal Study EUR-1008-M, and would allow for labeling of the EUR-1008 product in patients with EPI from the ages of one year through adulthood.

The above efficacy findings from EUR-1008M and 1009M support the approval and labeling of EUR-1008 for the treatment of steatorrhea due to EPI from CF (or other causes), in infants, pediatric, and adult patients, ages one year and older.

2.22 Safety Analysis and Conclusion

In consideration of the long and extensive safety experience with the PEPs, the Guidance assessed that it is not necessary to conduct long-term safety evaluations of the PEPs in support of the PEP NDAs; however, short-term safety evaluation is required during the clinical efficacy studies. Since PEPs act locally in the Gastrointestinal (GI) tract and are not absorbed, the Guidance further recommended that the safety variables assessed should focus predominantly on the monitoring of clinical signs and symptoms (i.e., AEs) during these clinical trials.

One exception to the relative safety of the PEPs is the association of fibrosing colonopathy with PEP use. Fibrosing colonopathy associated with PEP use is rare, and although the etiology has not been completely elucidated, it has been assumed to be related to high or inappropriate dosing of PEPs. Thus, the Cystic Fibrosis Foundation in conjunction with the FDA have recommended that PEP doses not exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal (FitzSimmons et al., 1997³; Borowitz et al., 2002⁴). Since publication of these recommendations, cases of fibrosing colonopathy have been reported only sporadically, and are unlikely to be reported during the relatively small clinical trials conducted in support of the PEP NDAs. Thus, continued monitoring for fibrosing colonopathy associated with PEP use is likely to best be performed through global safety surveillance.

Consistent with the Guidance, the safety evaluations performed for the EUR-1008 clinical development program focused predominantly on the monitoring of clinical signs and symptoms (i.e., AE assessments) during the short-term clinical efficacy and safety studies conducted with EUR-1008, and no long-term safety studies were performed.

The safety information submitted in this NDA submission includes an Integrated Summary of Safety (ISS), and safety information from individual clinical studies conducted with EUR-1008. The 120-Safety Update contains no new information, since EUR-1008 is not currently a commercially marketed product, and there were no ongoing studies during the review cycle.

The Review team concluded that this NDA submission provides evidence of short-term safety for the EUR-1008

2.3 Microbiology Analysis and Conclusion

The Microbiology Reviewer recommended an Approval action based on a satisfactory product quality microbiology review of the information submitted.

³ FitzSimmons SC, Burkhart GA, Borowitz D, Grand RJ, Hammerstrom T, Durie PR, Lloyd-Still JD, Lowenfels AB. High-dose pancreatic enzyme supplements and fibrosing colonopathy in children with Cystic Fibrosis. *N Engl J Med* 1997;336:1283-1289.

⁴ Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with Cystic Fibrosis. *J Pediatr Gastroenterol and Nutr* 2002;35(3):246-259.

The Reviewer noted that the product was non-sterile, and each of the four drug strengths of drug product has a microbial limits release specification of no more than 10^3 CFU/g of total bacteria, no more than 10^2 CFU/g of total combined yeasts and molds, and an absence of *Salmonella* and *Escherichia coli* species. Overall, the process validation, analytical procedures, and stability were found to be acceptable, and no microbiology deficiencies were identified in the review.

2.4 Virology Analysis and Conclusion

The active pharmaceutical ingredient in EUR-1008 pancrelipase, is derived from native pig pancreas tissue. One batch of pancrelipase DS requires glands from several thousand pigs, and such a large quantity of raw material has to be obtained from by-products of slaughtered pigs intended for use as food (these pigs have been certified as fit for human consumption). For this reason, the possibility of contamination of the starting material with viruses relevant to swine has to be considered. The viruses known to be present in swine include enveloped, non-enveloped, and emerging viruses. The reviewer had many concerns regarding the risk mitigation plan for these adventitious agents. These concerns were expressed to Nordmark in a regulatory letter (APPENDIX 1, items 1 through 5) dated 6/13/2008 from the Division of Therapeutic Proteins.

2.5 Non Clinical Pharmacology and Toxicology Analysis and Conclusion

Per the Guidance, given the long history of clinical use with the PEPs, the performance of new animal pharmacology studies with the active ingredient (pancrelipase) is not needed to support the EUR-1008 clinical development program. However, toxicology studies are needed if the excipients in the EUR-1008 DP are not classified as GRAS, and the toxicology program for the excipients should supply data from long-term studies in both rodent and non-rodent mammalian species, plus standard reproductive toxicity and genotoxicity information. Consistent with the Guidance, no new pharmacology or toxicology studies were conducted with EUR-1008 and no new non-clinical studies were submitted in the NDA submission, but the sponsor provided published information for the excipients in the clinical formulation of EUR-1008.

After review of this material it was concluded that from a non-clinical toxicology perspective EUR-1008 could be approved.

2.6 Clinical Pharmacology Analysis and Conclusion

Clinical pharmacology information submitted in the NDA submission consists of results from a bioactivity (BA) study and an *in vitro* stability study of EUR-1008 sprinkled on food.

2.61 Bioactivity study

The BA study was a single-center, randomized, open-label (OL), single-treatment, 2X2 cross-over, intubation study that evaluated the bioavailability of EUR-1008 in patients with chronic pancreatitis (CP) and EPI in gastric and duodenal aspirates under fed conditions (n=11). A single fixed dose of 75,000 USP lipase units (about 1,100 U/kg) was administered (as 3 X 20,000 U and 3 X 5,000 U capsules).

Eleven patients were entered and randomized in the study. One patient withdrew from the study, and two patients were excluded from the efficacy analysis (one outlier, and one

for violation of the Inclusion/Exclusion criteria), and eight patients were included in the Per Protocol efficacy analysis (all 11 patients were included in the safety analysis).

The difference in the amount of lipase recovered between the treatment groups (EUR-1008 + Food) and (Food only) was obtained. BA of EUR-1008 is the difference in amount of lipase recovered in duodenum and expressed as the fraction of the administered Eur-1008 dose (BA in %). Mean BA was reported to be 21.6% with a large inter-patient variation ranging from -51.9% to 71.4%.

The Reviewers determined that there were significant flaws and limitations to the conduct analyses and results of the BA study and therefore concluded that it was unacceptable.

2.62 Stability Study

Limitations in the results of this study were noted. It was determined that for the *in vitro* stability data, the data for two of the three batches of EUR-1008 capsules provided in this NDA were identical, and it was not clear if there were errors in the dataset. An information request for clarification was sent to the sponsor, but the sponsor has not responded to this request.

Therefore, the overall conclusion was that the clinical pharmacology section is not acceptable. The Clin Pharm comment was relayed to the Sponsor in the AE letter of June 16th, 2008 (deficiency 11, see APPENDIX 2)

2.7 Chemistry Manufacturing and Controls Analyses and Conclusion

The Product Reviewer performed separate reviews of the Drug Substance (DMF review) and the Drug Product. The overall assessment of the CMC data submitted in the NDA amendment was that the application is Approvable with deficiencies noted for both Drug Substance (DS) and Drug Product (DP).

2.71 Drug Substance (DS)

The DS is manufactured by the Nordmark (Nordmark Arzneimittel GmbH and Company, Uetersen, Germany), and Nordmark is the DMF holder (DMF #7090). The DMF has been cross referenced by Eurand in NDA 22-210. The DMF was most recently updated 13-July-2007, with additional information submitted December 2007. The manufacturing facility had never been inspected by the Agency at the time of this review (inspections are deferred pending resolution of outstanding CMC issues).

The overall findings of the CMC Reviewer were that a number of deficiencies identified for the manufacture of DS (deficiencies 6 to 18 in letter to Nordmark dated June 13, 2008, see APPENDIX 1), and that these deficiencies be communicated to the DS manufacturer (Nordmark) in a letter.

2.72 Drug Product (DP)

The DP EUR-1008 is manufactured by Eurand from the Nordmark-produced pancrelipase DS. The manufacturing process for DP entails

(b) (4)

EUR-1008 capsules contain 5,000, 10,000, 15,000 and 20,000 USP units (U) lipase. Capsules contain enteric-coated pancrelipase formulated with compendial excipients. The 10,000, 15,000, and 20,000 U capsules contain identical pancrelipase formulated beads. The 5,000 U capsule beads (“small coated beads”) are prepared with approximately dose-proportional pancrelipase excipients. The 10,000, 15,000, and 20,000 U capsules contain enteric-coated cylindrical mini-tablets having a diameter of (b) (4) mm and a thickness of (b) (4) mm; the 5,000 U capsules contain slightly smaller mini-tablets having a diameter of (b) (4) mm and a thickness of (b) (4) mm. The smaller size beads in the 5,000 U strength capsules offer the potential advantage of administration to young children by sprinkling the beads onto food. Stability studies with small beads mixed in foods (e.g., applesauce, pudding) support the use of various foods to administer the small beads (for up to 60 minutes).

The findings of the CMC Reviewer were that there were a number of deficiencies identified for the manufacture of DP, and that these deficiencies be communicated to the DP manufacturer (Eurand) in a letter (deficiencies 1 to 10 in AE letter dated June 16th, 2008, see APPENDIX 2).

3.0 Regulatory Conclusion and Action

I agree with the conclusions and recommendations of the Review Team and CDTL that this Application (NDA 22-210) is Approvable based on CMC and Clin Pharm deficiencies. I will communicate these deficiencies in a regulatory letter to the Sponsor.

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this page is the manifestation of the electronic signature.**

/s/

Daniel A. Shames
6/16/2008 02:39:51 PM
MEDICAL OFFICER
Deputy Office Director Memo

**Cross-Discipline Team Leader Summary Review of NDA 22-210
EUR-1008 (pancrelipase delayed-release capsules) for Exocrine Pancreatic Insufficiency**

Date: June 15, 2008

From: Anne R. Pariser, M.D., Clinical Team Leader
Division of Gastroenterology Products (DGP)

To: Daniel A. Shames, M.D., Deputy Director
Office of Drug Evaluation III (ODE III)

Identifying Information

NDA #: 22-210
Applicant: Eurand Pharmaceuticals, Inc.
Product name: EUR-1008 (pancrelipase delayed-release capsules)
Proposed Trade Names: Zentase, ZenPep, Zenase (trade name to be determined)
Submission date: December 14, 2007
Stamp date: December 17, 2007
PDUFA goal date: June 17, 2008
Formulation: EUR-1008 capsules for oral administration
Proposed indication: Treatment of exocrine pancreatic insufficiency (EPI)
Proposed regimen: Up to 2,500 lipase units per kg per meal, not to exceed
10,000 lipase units per kg per day

Recommended Regulatory Action: Approvable (AE) under 21 CFR 314.

I. Introduction, Background, and Regulatory History

A. Introduction

This submission is the initial New Drug Application (NDA) submission for EUR-1008. The Applicant is Eurand Pharmaceuticals, Inc. EUR-1008 is a New Molecular Entity (NME) that was granted priority review. This NDA submission was received on 17-December-2007, and the Prescription Drug User Fee Act (PDUFA) goal date is 17-June-2008.

B. Clinical Background

EUR-1008 (pancrelipase delayed-release capsules, Zentase) is an enteric-coated, delayed-release pancreatic enzyme product (PEP). EUR-1008 is an exogenous source of porcine-derived pancreatic enzymes intended to treat steatorrhea due to exocrine pancreatic insufficiency (EPI). EPI typically results from chronic loss of pancreatic tissue due a number of underlying diseases and conditions. Cystic Fibrosis (CF) is the most common cause of EPI in children, and chronic pancreatitis (CP) due to alcoholism or idiopathic pancreatitis is the most common cause of EPI in adults; however, there are a large number

of other causes, such as pancreatectomy. Clinical manifestations of EPI are predominantly steatorrhea, abdominal pain, weight loss, and nutritional problems (e.g., fat-soluble vitamin deficiencies) due to malabsorption. The main stay of therapy for steatorrhea and malabsorption due to EPI, regardless of cause, has been the administration of pancreatic enzyme replacement therapy (PERT) with exogenous sources of PEPs.

C. Regulatory History of Pancreatic Enzyme Products

PEPs are currently widely available in the United States (US) as non-prescription nutritional supplements or over-the-counter (OTC) medications, or by prescription. PEPs are available as enteric-coated/delayed-release and non-enteric coated formulations. These formulations are not considered to be interchangeable.

PEPs have been available in the US since prior to the Federal Food, Drug, and Cosmetic Act (The Act) of 1938. Most PEPs have been available since pre-Drug Efficacy Study Implementation (DESI; pre-1962), and have never undergone formal evaluation under Investigational New Drug (IND) applications or NDAs for efficacy or safety. Substantial variations among currently marketed products exist, including variations in formulation, dosage, and manufacturing processes, both between the different PEPs and within the individual PEP brands (from lot to lot and even within lots). Variations in drug potency that result from this product variability are known to exist, and may significantly affect the safety and effectiveness of the PEPs.

To address the problems with variations between the PEPs, the Food and Drug Administration (the Agency) published the following notices in the Federal Register (FR):

- In 1979, the Agency proposed establishing monographs for OTC PEPs.
- In 1985, recommendations of the PEP Advisory Review Panel were published that stated that OTC monographs would not be sufficient to regulate the PEPs, preclearance of each product to standardize enzyme bioactivity would be necessary, and PEPs should be made available by prescription only.
- In 1991, the Expert panel proposed that the FDA withdraw the 1985 proposed OTC rule, declared that the PEPs are not Generally Recognized as Safe (GRAS) and Generally Recognized as Effective (GRAE), and the PEPs are misbranded.
- In 1995, a Notice of Final Rule was published that stated all PEPs must obtain FDA approval (under NDA) in order to remain on the market.
- In 2004, the Notice of Requirement for NDA Approval was published that stated all PEPs must get NDA approval within the next four years (deadline 28-April-2008), and the expectation of the Agency was that only NDAs under 505(b)(2), not Abbreviated New Drug Applications (ANDAs), would be received. To be approved, PEP NDAs must meet the requirements for content and format of an

application as stated in 21CFR 314.50. A draft guidance for submitting NDAs for PEPs was also published at that time.¹

- In 2006, the Final Guidance for submitting NDAs for PEPs was published (heretofore referred to as “the Guidance”).²
- On October, 2008, Notice of Extension of the deadline was published, which stated that FDA would use enforcement discretion for the PEPs. Manufacturers must have an open IND by April 28, 2008, an NDA submitted by April 28, 2009, and an approved NDA by April 28, 2010 in order to continue marketing their products.

Note: These FR notices and the Guidance only apply to the currently-marketed, animal (porcine or bovine)-derived PEPs containing pancreatin and pancrelipase.

Currently, there is only one approved NDA for a PEP: Cotazyme, an immediate-release PEP (NDA 20-580); however, Cotazym is not currently marketed in the US. Thus, no approved PEPs are currently commercially available in the US under NDA.

D. Regulatory History of EUR-1008

The regulatory history for EUR-1008 is summarized as follows:

- A pre-IND meeting was held between the Applicant (Eurand) and the Division on 28-October-2004. The original IND submission for EUR-1008 was received by the Agency on 14-November-2005.
- The study protocol for the pivotal clinical study (EUR-1008-M), a double-blind, randomized, placebo-controlled, short-term safety and efficacy study in patients with CF and EPI seven years of age and older, was submitted by the Applicant for review on 02-March-2005, and the Division responded with comments and recommendations on 20-April-2005. Notable comments to the Applicant included that patients younger than seven years of age would need to be studied in the EUR-1008 clinical development program in order to allow labeling of the drug for younger patients.
- Protocol EUR-1009-M, an open-label, uncontrolled study of EUR-1008 administration to pediatric patients with CF, ages one to six years, was subsequently submitted. Comments back to the Applicant from the Division on 12-September-2006 were notable for the Division’s acceptance of the use of spot fecal fat samples as an assessment of effectiveness of EUR-1008 administration to young children, provided certain collection conditions were met (e.g., evidence for the validation of

¹ 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.” 2004.

² 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/6275f1nl.htm>> April 2006.

the spot fecal fat analysis to be used, and three random stool samples on three different days should be obtained and the average of the three used as the efficacy variable). In a subsequent teleconference (on 11-October-2006), the Applicant stated that samples had already been collected and assessments performed using a different method. The Division agreed to review the data as collected in the study; however, limitations were noted in the testing method, and this testing method will be considered only for this limited patient population.

- In a subsequent correspondence on 10-January-2006, the Division provided additional comments regarding the performance pediatric studies with EUR-1008, including the need for developing an age-appropriate formulation, and demonstrating the stability of the drug product after the capsules are opened and the contents mixed in soft food for administration to young children.
- EUR-1008 received Fast Track designation on 10-January-2007.
- Two pre-NDA meetings were held between the Applicant and the Division: one meeting on 13-April-2006 and one on 15-March-2007. During the first meeting, Chemistry, Manufacturing and Controls (CMC) issues were discussed. During the second meeting, Clinical, CMC, Clinical Pharmacology, and administrative issues were discussed, and the Applicant stated their intention to submit a rolling submission. Most of the remaining issues were review issues, and were deferred until submission and review of the NDA.
- During the NDA review cycle, the Applicant submitted a pediatric study deferral request, requesting that the evaluation of EUR-1008 in children from one month to one year of age be deferred until the post-marketing period. Comments regarding the proposed study design for this pediatric study were sent by the Division to the Applicant on 12-May-2008.

The primary review disciplines have all written review documents for this NDA, which should be consulted for more specific details. This memorandum summarizes selected information from these documents. The primary review documents relied upon include the following:

- Clinical Review: Marjorie F. Dannis, M.D., dated 15-June-2008.
- Statistical Review and Evaluation, Clinical Studies: Freda Cooner, Ph.D., dated 09-June-2008.
- Pharmacology/Toxicology Review: Ke Zhang, Ph.D., dated 01-May-2008.
- Clinical Pharmacology Review: Tien-Mien Chen, Ph.D., dated 11-June-2008.
- CMC Drug Product Review: Howard Anderson, Ph.D., dated 05-June-2008.
- CMC Drug Substance Review (review of Drug Master File [DMF]): Howard Anderson, Ph.D., dated June, 2008.
- Product Quality Microbiology Review: Stephen Langille, Ph.D., dated 22-May-2008.
- Virology Review: Ennan Guan, Ph.D., dated June, 2008.
- Facility Inspection Memorandum: Khairy Malek, M.D., dated 05-June-2008.

- Division of Medication Errors Prevention Proprietary Name Consultation Response, and Label and Labeling Review: Deveonne Hamilton-Stokes, dated 21-March-2008 and 07-May-2008, respectively.

Since an Approvable Action is recommended, no labeling or post-marketing commitments were negotiated during this review cycle, and no Advisory Committee was convened.

II. Chemistry, Manufacturing and Controls

CMC data have been extensively reviewed by the Product Reviewer (Howard Anderson, Ph.D.), Microbiology Reviewer (Stephen Langille, Ph.D.), and Virology Reviewer (Ennan Guan, Ph.D.). Please refer to the Drug Substance (DMF), Drug Product, Microbiology, and Virology reviews for more detailed information. Important issues identified in the Product, Microbiology, and Virology reviews are summarized as follows:

A. Product Review

The Product Reviewer (Dr. Anderson) performed separate reviews of the Drug Substance (DMF review) and the Drug Product. The overall assessment of the CMC data submitted in the NDA amendment was that the application is Approvable with deficiencies noted for both Drug Substance (DS) and Drug Product (DP).

1. Drug Substance (DS)

The DS is manufactured by the Nordmark (Nordmark Arzneimittel GmbH and Company, Uetersen, Germany), and Nordmark is the Drug Master File (DMF) holder (DMF #7090). The DMF has been cross referenced by Eurand in NDA 22-210. The DMF was most recently updated 13-July-2007, with additional information submitted December 2007. The results of a manufacturing facility inspection by the Agency were not available at the time of this review.

DS is derived from porcine pancreas glands harvested from pigs raised as human food. The glands are obtained from slaughterhouses in the European Union (EU), US, and Canada, and must be intended for pharmaceutical processing. The glands are frozen (-20°C), and remain frozen until they are processed by the manufacturer. The glands then undergo a (b) (4)

The resulting pancrelipase DS is to be used for manufacture of DP.

Dr. Anderson states in his review that characterization of the enzymes contained in the DS, including assays for amylase, lipase, protease (e.g, for a number of individual proteases, such as (b) (4) was performed. Detailed descriptions and validation reports for the analytical methods and enzyme assays used also were provided.

The overall findings of the Product Reviewer were that there were a number of deficiencies identified for the DS, including deficiencies in DS manufacturing and controls, and in the viral risk mitigation plan (see Virology review in section II.C. below). These deficiencies were communicated to the DS manufacturer (Nordmark) in a letter sent by the Division of Therapeutic Proteins (DTP) on 13-June-2008, which included the following comments on the deficiencies noted in the DS and Virology reviews (please see Dr. Anderson's and Dr. Guan's reviews for a complete listing of the deficiencies, and the letter to Nordmark for the final wording).

1. Nordmark has not provided an adequate description of the risk mitigation plan for adventitious agents, and was to provide the following:
 - a. The plan for animal disease surveillance, including how emerging viruses will be assessed and controlled.
 - b. A description of the sanitizing/cleaning procedures in place to prevent cross contamination. (b) (4)

 - c. Nordmark was asked to comment on the risk to product quality due to the potential infection of swine herds with parasites.
 - d. Nordmark was asked to clarify the difference in quality standards that distinguish porcine pancreatic glands for pharmaceutical use, since it is stated in the DMF that porcine pancreatic tissue must be designated for pharmaceutical processing (pharmaceutical use only), and not for human consumption.
 - e. Information submitted to the DMF states that pancreatic glands originate from the EU, Canada, or the US. Clarification from Nordmark was sought on whether pancreatic glands are harvested from swine born in these regions, or from swine imported into and slaughtered in these regions. If the latter is the case, then information on the country of origin of the swine is to be provided.
 - f. A summary of the pancreatic tissue vendor qualification/evaluation program for the last four years, including the names and dates of all pancreatic tissue vendor audits, quality systems evaluated, and a representative Health Certificate for animal by-products from each of the 12 approved vendors is to be provided.

2. Regarding the viral inactivation studies, Nordmark should address the following:

- a. Because of the inherent variability of the viral clearance studies, results should be obtained from two independent experiments (per ICH Q5A). However, the viral inactivation studies submitted were not performed as recommended, but rather used material from the same samples in duplicate and not from independent sources. Nordmark should provide information on the process's capacity to inactivate viruses from two independent experiments.
- b. While Nordmark provided two independent results for the spiking experiments using FCV, there is a large difference between the values reported. Nordmark additionally provided two calculations of overall FCV inactivation that differed by (b) (4) without indicating which number they believed best represents process capability. ICH Q5A states that the lower value should be used when evaluating data from independent experiments, which, in this case is consistent with the expected hardness of the virus. Nordmark is asked to elucidate the reasons for such great differences in inactivation of the virus, and consider performing additional studies to obtain a more consistent evaluation.
- c. Although an evaluation of the toxicity or interference of the test sample on the indicator cells appears to have been performed, no data were submitted to support the dilution factors used for the determination of viral titers. Nordmark should submit a brief description of the experiments performed, and the results obtained for the evaluation of assay interference for test samples from the three process steps assessed in the viral evaluation studies.
- d.

(b) (4)
- e. Nordmark should provide a detailed description of the procedures used for the evaluation of the (b) (4) and include a discussion on the similarity of the lab scale process to the commercial process.

3. Regarding the Q-PCR tests, DTP notes that without adequate information on the validation characteristics of the PCR tests, they are unable to fully assess the proposal. Nordmark should provide data supporting the validation characteristics of the Q-PCR tests used to estimate viral loads of both enveloped and non-enveloped viruses, and include in the response information on the selection of the primers, assay specificity,

sensitivity (LOQ/LOD), linearity and precision, system suitability criteria (including recovery), and the Standard Operating Procedures (SOPs) for the test protocols.

4. Regarding the viral infectivity tests, Nordmark should provide data supporting the validation characteristics of the viral infectivity assays used in the detection of both enveloped and non-enveloped viruses. This should include information on assay specificity, sensitivity (LOD), linearity and precision, and the SOPs for the test protocols, which should include a description of the system suitability criteria used to establish the validity of routine test results.
5. Regarding the specifications for adventitious agents:
 - a. Nordmark should revise their specifications to include routine testing for PPV infectivity for all lots, and tighten acceptance criteria to reflect recent manufacturing history.
 - b. DTP noted that while Nordmark has proposed to include testing to control the presence of HEV and PEV9 (SVDV), no testing was proposed for EMCV, Reo Virus, and Rota Virus. These viruses are known to cause infection through an oral route, and are not inactivated by the manufacturing process, suggesting that better risk mitigation strategies should be employed. Nordmark should submit a revised viral testing plan that includes monitoring of these non-enveloped viruses, and a calculation of estimated viral load per dose based on the limit of detection of the Q-PCR assay for HEV, EMCV, SVDV, Rota Virus, and Reo Virus.
 - c. DTP states that although Nordmark plans to measure PPV genome equivalents, DTP does not believe this information will be useful in establishing a robust correlation between genome equivalents and infectivity, and, therefore, does not consider this study necessary.
 - d. Nordmark should establish a specification for infectious PCV 1 and PCV 2. DTP believes that the final product should be free of infectious PCV as Nordmark's historical data have shown.
 - e. DTP states that based on the ability of the process to inactivate enveloped viruses, Nordmark has proposed not to set specifications for the presence of enveloped viruses. However, DTP notes that it is difficult to validate the absence of adventitious agents, that Nordmark's control of the procedures followed in the slaughterhouses is very limited, and that the limit of detection of viral genomic equivalents may be near the process's capacity to inactivate viruses. Nordmark should provide a calculation of estimated enveloped viruses per dose based on the limit of detection of the Q-PCR assay, and discuss how their proposal provides an appropriate level of control for enveloped viruses. Given the situation, DTP believes that setting action limits and specification for the presence of viral genomes and

infectious viruses, respectively, provides better control of these viruses, and requests Nordmark's comments on this proposal.

6. DTP noted that Nordmark is currently using the USP lipase reference standard and the USP amylase and protease reference standards to measure enzymatic activities in the DS. DTP has the following recommendations regarding the reference standard:
 - a. Nordmark should develop an internal reference standard that reflects the commercial manufacturing process to be used, in addition to the USP pancrelipase reference standard, in all release and stability testing.
 - b. Nordmark should develop a rigorous qualification program aimed at ensuring that the quality attributes of the internal reference standard are maintained when new internal reference standards are required and manufactured.
 - c. Nordmark should provide the details of the storage conditions and expiration dating for all reference standards.
7. DTP recommends that Nordmark consider establishing and justifying a specification for total starting gland weight used for each manufacturing run as it relates to DS lipase yield.
8. DTP acknowledges Nordmark's plans to re-examine the production process. Nordmark should conduct the study on three consecutive batches and submit a summary of the results to the DMF, and specify when they plan to initiate and complete these studies.
9.  (b) (4)
 DTP notified Nordmark that rejected batches may not be reworked or reprocessed and product released under an approved NDA without prior FDA approval.
10.  (b) (4)
11.  (b) (4)
12. As part of the RP-HPLC assay validation, Nordmark should determine how much protein is retained on the column.

13. Nordmark should establish and justify a specification for water content for DS release and stability testing.

14. Nordmark demonstrated that the addition of (b) (4)

[Redacted]

15. To demonstrate that the pancreatin DS matrix does not interfere with the lipase enzyme assay, Nordmark (b) (4)

[Redacted]

16. Nordmark has not submitted sufficient information in the DMF to evaluate the qualification program for the lipase olive oil substrate. Nordmark should provide qualification results for olive oil testing, and establish and justify specifications for critical olive oil components.

17. Nordmark should provide a copy of the pancrelipase DS label.

18. Nordmark should clarify the storage conditions and expiration date that are proposed for the DS, clarify how they will ensure that the DS is transported under the appropriate conditions, and provide shipping validation data.

2. Drug Product (DP)

The DP EUR-1008 is manufactured by Eurand from the Nordmark-produced pancrelipase DS. The manufacturing process for DP entails (b) (4)

[Redacted]

EUR-1008 capsules contain 5,000, 10,000, 15,000 and 20,000 USP units (U) lipase. Capsules contain enteric-coated pancrelipase formulated with compendial excipients. The 10,000, 15,000, and 20,000 U capsules contain identical pancrelipase formulated beads. The 5,000 U capsule beads (“small coated beads”) are prepared with approximately dose-proportional pancrelipase excipients. The 10,000, 15,000, and 20,000 U capsules contain enteric-coated cylindrical mini-tablets having a diameter of (b) (4) mm and a thickness of 2.2 mm; the 5,000 U capsules contain slightly smaller mini-tablets having a diameter of (b) (4) mm and a thickness of (b) (4) mm. The smaller size beads in the 5,000 U strength capsules

offer the potential advantage of administration to young children by sprinkling the beads onto food. Stability studies with small beads mixed in foods (e.g., applesauce, pudding) support the use of various foods to administer the small beads (stability for up to 60 minutes – see Clinical Pharmacology review in section IV.B. below).

EUR-1008 capsules are enteric-coated with hypromellose phthalate (HPMCP). HPMCP is commonly used in oral pharmaceutical formulations since it is insoluble in gastric fluids, and will swell and dissolve in the upper intestine. (b) (4)

Other excipients were chosen based on favorable disintegration rates. All EUR-1008 excipients are compendial grade (USP/NF grade), except FDC Blue 2, which is 21 CFR compliant. Dr. Anderson notes that sufficient information and controls are in place to ensure excipient quality. The unit composition of EUR-1008 to-be-marketed product (TBMP) is summarized in the following table (copied from Dr. Anderson’s review):

Table 1: Unit Composition of EUR-1008 TBMP

Capsule Strength (U lipase)	Unit Composition/Capsule (mg)				Reference to Standard	Function
	5,000	10,000	15,000	20,000		
Component						
Pancrelipase	(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP/DMF	DS (API)
Croscarmellose sodium	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
Hydrogenated castor oil	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
Colloidal silicon dioxide	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
Microcrystalline cellulose	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
Magnesium stearate	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
Hypromellose phthalate	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
Talc	(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP	(b) (4)
Triethyl citrate	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
Bead/Tablets Weight						
HPMC Capsule	(b) (4)	(b) (4)	(b) (4)	(b) (4)	DMF	(b) (4)
Carrageenan	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
Potassium chloride (KCl)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP	(b) (4)
Titanium dioxide	(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP	(b) (4)
Hypromellose	(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP	(b) (4)
Carnauba wax or talc	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF or USP	(b) (4)
Water	(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP	(b) (4)
Yellow ferric oxide	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
Red ferric oxide	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF	(b) (4)
FDC Blue 2	(b) (4)	(b) (4)	(b) (4)	(b) (4)	21 CFR 74 21 CFR 82	(b) (4)
Total Capsule Weight	117.9	208.9	313.4	388.9		

Note: Phthalic acid is a breakdown product of the hypromellose phthalate coating material, and the phthalic acid peak on RP-HPLC is a stability indicating peak in respect to the enteric coating (is measured as part of the stability protocol). Eurand has found that the phthalic acid content in stability and clinical lots ranges from (b) (4). During the review cycle, Health Canada notified FDA that monoethyl phthalate and its glucuronide (a metabolite of diethyl phthalate) had been detected in the urine of CF patients, which is

thought to be from the enteric coating of delayed-release PEPs. More information is required from the Applicant regarding the hypromellose phthalate coating raw material, and DTP will request that the Applicant provide detailed information regarding the manufacture of the hypromellose phthalate used for enteric coating of the beads.

Dr. Anderson notes that characterization of physicochemical and biological properties of lipase, protease, and amylase activities have been carried out on clinical trial lots of DS and DP. Validation of analytical methods has been provided, and in general, validation is acceptable and data are presented to support that enzyme reactions are linear with respect to time and specific activity is measured. Spiking DS with excipients demonstrate that excipients do not affect the performance of enzyme activity assays; however, further information is required for the lipase assay. Stability data to support 18 months of product storage are also provided.

The overall findings of the Product Reviewer were that there were a number of deficiencies identified for the manufacture of DP, and that these deficiencies need to be communicated to the DP manufacturer (Eurand) in a letter. These deficiencies are summarized as follows (please see Dr. Anderson's review for a complete listing of the deficiencies, and the Approvable [AE] letter to Eurand for the final wording):

1. Process validation of the intended full commercial batch size for each manufacturing step will be completed prior to marketing. Eurand should provide complete information on three consecutive commercial scale DP conformance lots, and indicate when validation studies will be initiated and completed.
2. During the review cycle, Health Canada notified FDA that monoethyl phthalate and its glucuronide (a metabolite of diethyl phthalate) had been detected in the urine of CF patients. More information is required from the Applicant regarding the hypromellose phthalate coating raw material, and DTP is requesting that Eurand provide detailed information regarding the chemistry, manufacturing, and controls for the hypromellose phthalate used for enteric coating of the beads.
3. There is insufficient stability to support the requested dating period of (b) (4) for DP. ICH Q5C indicates that expiry dating for biological products should be set using real time, real temperature stability data. Therefore, the data provided supports an 18-month expiry.
4. Eurand should specify how long excursions up to 30°C are permitted, and provide data to support the excursions.
5. Eurand will be notified that the Nordmark DMF #7090 has been reviewed in support of NDA #22-210 and found to contain deficiencies, and that a letter has been sent to Nordmark listing the deficiencies. Nordmark should address the deficiencies and update the DMF by directly submitting the information to the DMF. Eurand is to notify the FDA when Nordmark has submitted the requested information.

6. Insufficient information was submitted to evaluate the qualification program for the lipase olive oil substrate. Eurand should provide qualification results for olive oil testing, and establish and justify specifications for critical olive oil components.
7. Regarding release and stability specifications, acceptance criteria should be established based on manufacturing history process capability and clinical experience. DTP recommends that:
 - a. Acceptance criteria for the protease and amylase activity should be tightened to reflect actual manufacturing capability, for both final and intermediate DP.
 - b.  (b) (4)
 - c. Eurand should establish a release specification for phthalic acid for the four DP strengths, and provide a justification for the acceptance criteria chosen.
 - d. Acceptance criteria for the Uniformity of Dosage Units should be the same for the clinical/stability lots and for the lots to be marketed. The proposed weight limit of  (b) (4) of target weight fill is too broad to ensure consistent manufacturing of EUR-1008, and should be revised.
 - e. A specification for water content for DP release and stability testing should be established and justified.
8. As part of the RP-HPLC assay validation, Eurand should determine how much protein is retained on the column.
9. The certificate of analysis for the RP-HPLC pancrelipase reference standard release testing only includes specifications for peak areas. Eurand should develop a rigorous qualifications program aimed at ensuring that the quality attributes of the internal reference standard are maintained when new internal reference standards are required and manufactured. DTP also recommends that an internal reference standard that reflects the commercial manufacturing process be used, in addition to the pancrelipase DS reference standard, in all release and stability testing.
10. The working standard certificate of analysis for batch #P13309305 has two different USP lipase specific activities depending on the USP reference standard used. Eurand should develop and implement a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the reference standard.

3. Product Review Summary

The overall assessment of the Product Reviewer (Dr. Anderson) for the CMC data submitted in the NDA is that the application is Approvable (AE) with deficiencies noted for both DS and DP. The deficiencies for DS and DP are to be communicated in separate letters to the DS manufacturer (Nordmark), and to the DP manufacturer (Eurand), respectively.

B. Microbiology Review

The Microbiology Reviewer (Dr. Langille) recommended an Approval action based on a satisfactory product quality microbiology review of the information submitted.

Dr. Langille noted that the product was non-sterile, and each of the four drug strengths of drug product has a microbial limits release specification of no more than 10^3 CFU/g of total bacteria, no more than 10^2 CFU/g of total combined yeasts and molds, and an absence of *Salmonella* and *Escherichia coli* species. Overall, the process validation, analytical procedures, and stability were found to be acceptable, and no microbiology deficiencies were identified in the review.

The Microbiology Reviewer did not recommend any comments relating to the microbiology information be communicated to the Applicant.

C. Virology Review

The Virology Reviewer (Dr. Guan) performed a detailed review of the virology information submitted in the NDA (information located in the DMF for DS). Dr. Guan's findings are as follows:

The active pharmaceutical ingredient in EUR-1008, pancrelipase, is derived from pig pancreas tissue. One batch of pancrelipase DS requires glands from several thousand pigs (approximately 50,000 pigs for a batch using up to (b) (4) kg of frozen glands), and such a large quantity of raw material has to be obtained from by-products of slaughtered pigs. At the slaughterhouses, pigs introduced for slaughter are declared as fit for human consumption after they have been found to be healthy by visual inspection only. The gland quality is monitored at receiving, and includes visual appearance, veterinarian certification, and demonstration of cold chain maintenance during transportation and storage. The glands are then quarantined for four weeks to avoid introduction into manufacturing of glands that are associated with a disease outbreak in the source pigs. Given the source of the material, the possibility of contamination of the starting material with viruses relevant to swine has to be considered. The viruses known to be present in swine include enveloped, non-enveloped, and emerging viruses listed and considered in detail in Dr. Guan's review.

(b) (4) viral inactivation steps are involved in the DS manufacturing process, (b) (4) To mitigate the risk from adventitious agents, the manufacturer (Nordmark) performed an evaluation of the capacity of the manufacturing process to remove viruses (viral clearance and clearance/inactivation studies and viral load testing).

The viral clearance studies include the selection of model viruses for viral clearance and validation. Dr. Guan's assessment was that the model viruses selected cover the physical and chemical properties of all relevant potential viral pathogens associated with pancrelipase and most of the relevant viruses. The general plan is suitable for validation of the manufacturing process for viral clearance (in accordance with ICGH Q5A guidelines).

For the viral inactivation/clearance studies, the manufacturer provided information in the submission on the viral inactivation procedures for the (b) (4)

The results showed that:

- No infectious virus was observed after the (b) (4) inactivation step; however, limitations were noted in the data submitted, including incomplete reports of the studies performed, use of (b) (4) step (which may cause viral inactivation on its own, and will interfere with the cell-based infectivity assays), and no details as to the procedures and protocols used to assess viral inactivation for non-enveloped viruses.
- Inactivation of enveloped viruses by (b) (4) showed that there was an immediate inactivation of virus by (b) (4) (and by the pancreatic enzymes present in the pancreas homogenate). There was no significant inactivation of non-enveloped viruses with the exception of Rota virus, which was significantly reduced.
- No viral inactivation information was provided for the (b) (4)
- Overall, the viral inactivation results showed that a combination of the (b) (4) steps can provide a relatively robust inactivation of enveloped viruses, and the non-enveloped virus Rota virus was significantly reduced; however, no or inadequate reductions in some other non-enveloped viruses (e.g., FCV, a model for hepatitis E virus [HEV]) were seen.

Testing of input viral loads for enveloped viruses was performed using selected viruses (e.g., influenza A) to model the capacity of the manufacturing process to inactivate enveloped viruses. Results of the testing showed that the model viruses were negative in all 16 representative batches run using titers of genomic equivalents determined by Q-PCR assays. Dr. Guan noted that the validation characteristics of the PCR-based test used to evaluate viral load were not provided; however, the available information for the assay noted that it was an insensitive test (assay sensitivity appears to be approximately (b) (4) logs of viral particles/gram of product), and given the insensitivity of the assay, the inability to detect viruses by this method does not mean that viruses are not present.

Non-enveloped viral loads were also tested by Q-PCR using 50 DS batches for the presence of zoonotic viruses (e.g., HEV) and non-zoonotic viruses (e.g., porcine parvovirus [PPV]). Assay validation characteristics were also not provided, and Dr. Guan stated that she was unable to evaluate the results for Q-PCR testing because of the lack of this information. However, given the expected assay sensitivity and the level of viral inactivation demonstrated for enveloped viruses, Dr. Guan stated that there appears to be a

large gap in the ability to control the viral levels in the final product. Dr. Guan recommended that the sponsor develop more sensitive assays for quantitation of non-enveloped viruses.

The overall assessment of Dr. Guan was that although the manufacturing process may provide for an acceptable capacity for viral inactivation of enveloped viruses and inadequate viral inactivation for non-enveloped viruses, without additional data (e.g., assay validation characteristics), the results are not assured.

Infectivity testing by cell-based assays for non-enveloped viruses was also performed. Using these assays, Nordmark showed that negative infectivity results were observed for all viruses tested, except for PPV and PCV 1 and 2. HEV was not detected, but DTP did not feel the results of this test were reliable.

DTP's assessment of Nordmark's routine viral testing plan, which plans to routinely test for a limited number of viruses (PPV, HEV and PEV9) was that the plan is inadequate, and did not sufficiently address risk. DTP recommended that the testing plan include routine testing of all viruses thought to have the capacity to infect humans, to routinely test infectivity of PCV 1 and 2, and to address risk mitigation for emerging viruses, animal disease surveillance, and sanitizing procedures for equipment.

Thus overall, it was the assessment of the Virology Reviewer that there are number of deficiencies in the DS manufacturer's viral risk mitigation plan. Dr. Guan recommended that these deficiencies be communicated to the DS manufacturer (Nordmark) in a letter. The virology deficiencies, along with the CMC DS deficiencies, were sent in a letter by DTP to Nordmark on 13-June-2008 (a listing of all of the DS deficiencies is located in section II.A.1., Drug Substance review, above.)

III. Nonclinical Pharmacology and Toxicology

Nonclinical pharmacotoxicology data have been reviewed in detail by the Animal Pharmacotoxicology Reviewer (Ke Zhang, Ph.D.); please refer to this review for more information.

PEPs have been widely used in clinical practice as treatments for EPI since prior to 1938, and there is a large amount of clinical experience with these products in human patients. Per the Guidance, given the long history of clinical use with the PEPs, the performance of new animal pharmacology studies with the active ingredient (pancrelipase) is not needed to support the EUR-1008 clinical development program. However, toxicology studies are needed if the excipients in the EUR-1008 DP are not classified as GRAS, and the toxicology program for the excipients should supply data from long-term studies in both rodent and non-rodent mammalian species, plus standard reproductive toxicity and genotoxicity information. Consistent with the Guidance, no new pharmacology or toxicology studies were conducted with EUR-1008 and no new non-clinical studies were submitted in the NDA submission. The non-clinical information provided by the Applicant

in the submission was from the published literature for the excipients in the clinical formulation of EUR-1008.

Dr. Zhang notes that the Applicant also submitted an IND (70,563) with EUR-1008 on 11-November-2005, and based on the pharmacology review of this IND, all excipients in the clinical formulation of EUR-1008 are present in FDA-approved oral drug products. The estimated daily intake of these excipients is less than the amounts present in the FDA-approved products except for three excipients: hypromellose phthalate (^{(b) (4)} mg/capsule), triethyl citrate (^{(b) (4)} mg/capsule), and hypromellose (^{(b) (4)} mg/capsule) if 25 capsules are consumed daily. These excipients are present in higher amounts than the allowable levels in the FDA-approved products for a single-dose, which are hypromellose phthalate 302 mg, triethyl citrate 20 mg, and hypromellose 480 mg.

The Applicant did not provide the maximum daily allowable levels for these excipients in the original NDA submission. The Division requested in the 74-day to the Applicant that the maximum daily allowable levels in the FDA-approved products for hypromellose phthalate, triethyl citrate, and hypromellose be provided, and that the Applicant justify the safety of these excipients by published literature or by supporting toxicology studies. In response to this request, the Applicant provided the following:

- Hypromellose or hydroxypropyl methylcellulose (HPMC) is considered as a food additive permitted for direct addition to food for human consumption in 21 CFR 172.874. HPMC is one of the five modified celluloses (methyl cellulose, methyl ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, and sodium carboxymethyl cellulose) that were reviewed by the Joint FAO/WHO Expert Committee on Food Additives (thirty-fifth report, 1990), and the group established an acceptable daily intake (ADI) of up to 25 mg/kg for these five modified celluloses. The report also indicated that the modified celluloses have been used as laxatives at doses of 5 to 30 g/day and that the “amount ingested in studies in human did not exceed 30 g per person per day, which has been recommended by the United States National Research Council as the upper safe level of dietary fibre in general”. These modified celluloses were also not carcinogenic in long-term carcinogenicity studies in mice and rats, or embryotoxic in mice, rats, and rabbits based on this report.

The maximum daily intake of HPMC from EUR-1008 is ^{(b) (4)} mg/day, which is much less than the recommended level.

- Triethyl citrate is considered as GRAS under 21 CFR 184.1911 when used as a flavoring agent, a solvent or vehicle, or a surface-active agent. An ADI of up to 10 mg/kg was established by the Joint FAO/WHO Expert Committee on Food Additives. This is much higher than the estimated maximum daily intake of triethyl citrate from EUR-1008 of ^{(b) (4)} mg/day (or ^{(b) (4)} mg/kg/day if 50 kg body weight is assumed).
- Hypromellose phthalate or hydroxypropyl methylcellulose phthalate (HPMCP) is a polymer consisting of approximately 24% phthalyl-, 8% hydroxypropoxy-, and 22% methoxy-substitution of the cellulose backbone. The approved oral formulations of

HPMCP by the FDA are up to 302.4 mg/unit dose, but the maximum daily acceptable oral level is not available. The estimated maximum daily intake of HPMCP from EUR-1008 is (b) (4) mg/day (or (b) (4) mg/kg/day if 50 kg body weight is assumed). The Applicant provided published toxicology studies to justify the safety of HPMCP at this dose, including 30-day and six-month oral toxicity studies in rats and a 27-week oral toxicity study in dogs. The no-effect level in these studies was identified as 4.5 g/kg/day in the 30-day rat study, 6.0 g/kg/day in the six-month rat study, and 3.0 g/kg/day in the 27-month dog study. Dr. Zhang assessed in his review that these findings would provide a sufficient safety margin for the estimated maximum daily intake of HPMCP from EUR-1008 of (b) (4) mg/kg/day.

Thus, Dr. Zhang's overall conclusion from the non-clinical review of the information submitted in the NDA was that approval of the EUR-1008 NDA is recommended. Dr. Zhang additionally recommended that the proposed labeling be revised to include the following:

- Wording in the Pregnancy section be revised to: Category C. "Animal reproduction studies have not been conducted with Zentase. It is not known whether Zentase capsules can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Zentase capsules should be given to a pregnant woman only if clearly needed."
- In the Carcinogenesis, Mutagenesis and Impairment of Fertility section, the paragraph referring to a study by Nemeč et al should be removed.

Since EUR-1008 is not recommended for Approval during this review cycle, the proposed labeling changes will be planned for negotiation with the Applicant should EUR-1008 receive an Approval action during a subsequent review cycle.

IV. Clinical Pharmacology

The clinical pharmacology data have been extensively reviewed by the Clinical Pharmacology Reviewer (Tien-Mien Chen, Ph.D.). Please refer to this review for more detailed information. Clinical pharmacology information submitted in the NDA submission is limited to the results obtained in a single, bioavailability (BA) study PR-001. The Applicant also submitted the results of an *in vitro* stability study of EUR-1008 sprinkled on food. Dr. Chen's review is limited to the review of these two studies.

A. Bioavailability Study

The bioavailability (BA) study was a single-center, randomized, open-label (OL), single-treatment, 2 X 2 cross-over, intubation study that evaluated the bioavailability of EUR-1008 in patients with chronic pancreatitis (CP) and EPI in gastric and duodenal aspirates under fed conditions. A single fixed dose of 75,000 USP lipase units (about 1,100 U/kg) was administered (as 3 X 20,000 U and 3 X 5,000 U capsules). The BA study procedures were as follows:

- Patients were fasted beginning at midnight of the day preceding the procedure (Day 1).
- On Day 2, a modified Dreiling tube (without balloon) was placed under fluoroscopy, and Baseline intraduodenal aspirations were performed. Patients then received either a liquid meal of two 240 mL Ensure Plus alone, or EUR-1008 capsules opened and contents mixed in Ensure Plus in each of the two treatment periods. Aspirations/collections were then started about five minutes later at 15-minute intervals for three hours.
- Day 3 was a wash-out period.
- On Day 4, the Day 2 procedures were repeated with the alternative treatment (patients who received Ensure + EUR-1008 on Day 2 received Ensure alone on Day 4, and patients who received Ensure alone on Day 2 received Ensure + EUR-1008 on Day 4).

Eleven patients were entered and randomized in the study. One patient withdrew from the study, and two patients were excluded from the efficacy analysis (one outlier, and one for violation of the Inclusion/Exclusion criteria). Thus, eight patients were included in the Per Protocol efficacy analysis (all 11 patients were included in the safety analysis). Important issues identified in the review of this study are summarized as follows:

- The data from the eight patients who completed the study were evaluated (Per Protocol analysis). The difference in the amount of lipase recovered between the treatment periods (EUR-1008 + Food) and (Food only) was obtained. The BA of EUR-1008 is the difference in amount of lipase recovered in the duodenum and expressed as the fraction of the administered EUR-1008 dose (BA in %). Mean BA was reported to be 21.6% with a large inter-patient variation ranging from -51.9% to 71.4%.
- When a subpopulation of patients (Patients 2 and 7) with low duodenal pH (<4.0) was excluded (EUR-1008 is designed to release lipase at pH>5.0), the mean BA in the remaining six patients was 33.7%, with a smaller inter-patient variation ranging from 10.8% to 71.4%.
- Limitations in the study were noted by Dr. Chen, as follows:
 - The quantity of lipase recovered in one patient following administration of food only was approximately 35,000 U, which was substantially greater than the lipase recovered (zero U) following administration of 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, and raises questions about the reliability of the overall study results.
 - It is not clear how the methodology ensures that the lipase recovered from the duodenal aspirations represents the total lipase available in the duodenum. This information was requested during the review cycle, but the Applicant has not responded to this request.

- The number of patients available for evaluation is too small (n=8) in view of the high variability observed in the study.
- Some patients had very high endogenous lipase levels at Baseline and under fed conditions (giving food only). In the opinion of Dr. Chen, it appeared that a better approach would have been to select and enroll only patients with significant pancreatic enzyme insufficiency, and to have had an assay method specific to exogenous pancreatic lipase.

Dr. Chen's overall conclusion was that the BA study is not acceptable due to questions about the reliability of the data, unclear methodology regarding lipase recovery from duodenal aspirations, the small size of the study and high variability of the results, the enrollment of patients with high Baseline lipase levels, and the lack of a specific assay method for exogenous pancreatic lipase.

B. *In Vitro* Stability

The *In Vitro* Stability Study (Stability Study) was performed to evaluate the influence of the contact of different common types of baby foods on "gastroresistance" of EUR-1008 capsules. The study was conducted using the contents of 5,000 U capsules, since this strength is specifically intended for administration to infants and young children, and is likely to be administered after mixing in soft foods.

The results from this study show acceptable stability data for EUR-1008 content when mixed with ten types of food (pH<5.0) for 60 minutes, such as commercial preparations of applesauce, bananas, pears, pudding, or yoghurt. These results support the Applicant's proposed labeling statement of "If necessary, capsules can also be sprinkled on relatively acidic soft food (i.e., commercially available preparations of bananas, pears and applesauce, grated apple with sugar and lemon, smashed banana with sugar and lemon)." However, limitations in the results of the study were noted. It was noted that for the *in vitro* stability data, the data for two of the three batches of EUR-1008 capsules provided in this NDA were identical, and it was not clear if there were errors in the dataset. An information request for clarification was sent to the Applicant, but the Applicant has not responded to this request.

C. Conclusions

Dr. Chen's overall conclusion was that the clinical pharmacology section of this NDA is not acceptable for the following reasons:

- For the *in vivo* intubation study (PR-001; BA study), the study is not acceptable due to questions about the reliability of the data, unclear methodology for total lipase recovery from duodenal aspirations, small size of the study and high variability of the results, enrollment of patients with high Baseline lipase levels, and the lack of a specific assay method for exogenous pancreatic lipase.

- For the *in vitro* stability study, it was noted that the *in vitro* stability data for two of the three batches of EUR-1008 capsules provided in this NDA were identical, and it was not clear if there were errors in the dataset. An information request for clarification sent to the Applicant had not been responded to by the end of the review cycle.

Dr. Chen stated that the concern with the *in vitro* stability data is an Approvability issue that should be included in the action letter to the Applicant. The other comments regarding the BA study are not Approvability issues, and should be conveyed to the Applicant in a separate letter.

V. Clinical/Statistical

The clinical data have been extensively reviewed by the Clinical Reviewer (Marjorie Dannis, M.D.) and the Statistical Reviewer (Freda Cooner, Ph.D.). Please refer to the Clinical and the Statistical Reviews for more detailed information.

There is no previous clinical experience with the current formulation EUR-1008; however, there is considerable clinical experience with similar formulations of porcine-derived PEPs manufactured by Eurand (Ultrase® marketed by Axcan Pharmaceuticals, and Lipram® by Global Pharmaceuticals) and with commercially available porcine-derived PEPs made by other manufacturers.

A. Clinical Studies

The NDA submission contains efficacy and safety information from two short-term clinical safety and efficacy studies in which EUR-1008 was administered to pediatric and adult patients with CF, and one clinical bioavailability (BA) study in adult patients with chronic pancreatitis. The most important clinical study for demonstrating efficacy was EUR-1008-M. The two short-term efficacy and safety studies are:

1. Study EUR-1008-M (Pivotal Study) was a multi-center, randomized, double-blind (DB), placebo-controlled, two-treatment, cross-over study of EUR-1008 administered to 34 patients with CF and EPI, ages 7 to 23 years. The objectives of the study were to describe the short-term (approximately 20 to 35 days of EUR-1008 treatment) efficacy and safety of EUR-1008. Efficacy was assessed by the difference in a 72-hour fecal fat collection (CFA) on EUR-1008 treatment as compared to placebo treatment.
2. Study EUR-1009-M (Pediatric Study) was a multi-center, non-randomized, open-label (OL), uncontrolled, single-arm, short-term (14-day), safety and efficacy study of EUR-1008 in 19 infants and children with CF and EPI, ages one to six years. The objectives of the study were to compare measures of fat malabsorption (by spot fecal fat testing) while patients were receiving EUR-1008 or their usual PEP treatment. Per Cystic Fibrosis Foundation (CFF) recommendations that young children with CF not undergo wash-out, placebo, or no-treatment periods, all patients were treated with either their usual PEP treatment or EUR-1008 throughout the duration of the study.

The Clinical Reviewer (Dr. Dannis) extensively reviewed the efficacy and safety information from these two studies in the Primary Clinical Review, and the Statistical Reviewer (Dr. Cooner) conducted statistical analyses of the efficacy results from EUR-1008-M only. In addition, Dr. Dannis reviewed the available safety data from the BA study (the efficacy review for the BA study was deferred to the Clinical Pharmacology Reviewer Dr. Chen; see section IV, above).

B. Efficacy Results

The primary efficacy endpoint in the pivotal study EUR-1008-M was the comparison of percent coefficient of fat absorption (%CFA) to a %CFA on no-active (placebo) treatment. %CFA is determined from a 72-hour stool collection while the patient is consuming a high-fat diet, and is calculated by:

$$\%CFA = \frac{[\text{Fat intake (g/day)} - \text{Fat excretion (g/day)}]}{\text{Fat intake (g/day)}} \times 100$$

A change in %CFA of 30% or greater in severely affected patients (patients with a no-treatment %CFA of 40% or less) is considered to be clinically meaningful. No accepted change in %CFA has been established for patients with no-treatment %CFA greater than 40%. Change in %CFA with active treatment is expected to be larger in more severely affected patients than in patients with higher no-treatment %CFAs, as the more severely affected patients have a greater capacity to respond to treatment. Thus, the overall (mean) results of the studies are expected to be at least partly dependent on the severity of patients (by no-treatment/placebo %CFA at Baseline) enrolled in the studies.

The short-term efficacy and safety study in young children (EUR-1009-M) evaluated spot fecal fat testing using three stool samples collected on three separate days, since 72-hour stool collections are difficult to obtain in young children. Spot fecal fat testing is not considered to be a definitive measure of effectiveness; however, spot testing was felt to be acceptable in this patient population for providing evidence of responsiveness (fecal fat content <30%), which could allow for extrapolation of the CFA results from older children and adults to a younger population.

1. Study EUR-1008-M

The Pivotal Study EUR-1008-M was a multi-center, randomized (1:1 to treatment sequence), DB, placebo-controlled, two-treatment, cross-over study of EUR-1008 administered to 34 patients with CF and EPI, ages 7 to 23 years. The objectives of the study were to describe the short-term (approximately 20 to 35 days of EUR-1008 treatment) efficacy and safety of EUR-1008. The primary efficacy endpoint was the difference in a 72-hour fecal fat collection (CFA) during EUR-1008 treatment as compared to placebo treatment.

EUR-1008 was administered to all patients in the study in a dose range that complied with CFF recommendations. Doses of EUR-1008 were not to exceed 2,500 lipase units/kg/meal or 10,000 lipase units/kg/day (for three meals and two snacks per day; snack-dose is half

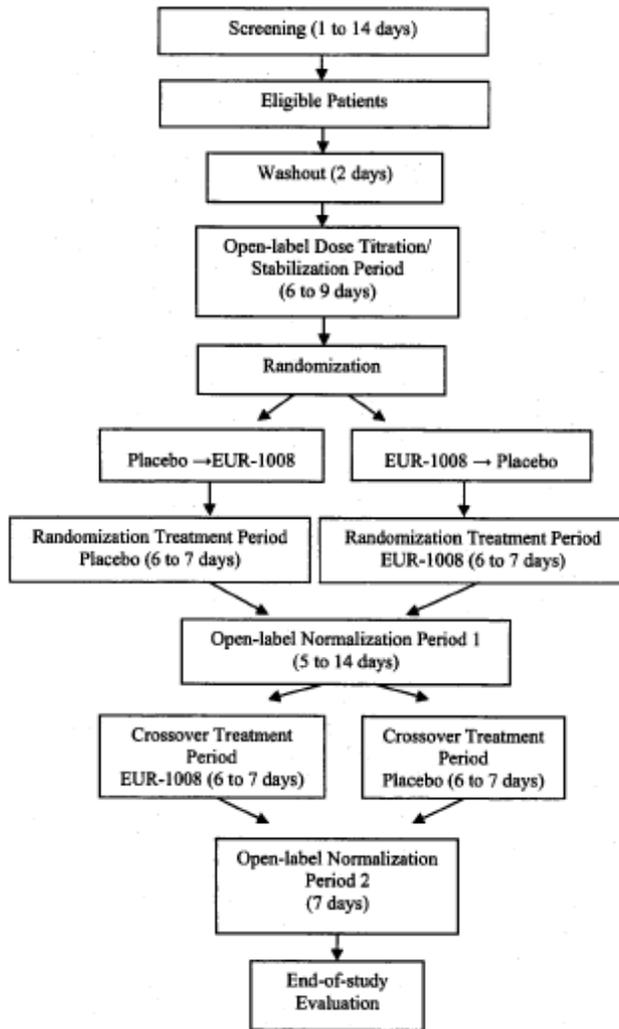
the meal-dose of PEP). Per-patient doses were obtained by combining all four unit strengths of EUR-1008 (5,000, 10,000, 15,000, and 20,000 U capsules) intended for commercialization.

The study design consisted of the following periods:

- Screening Period (1 to 14 days): Patients were continued on their usual commercially available PEP treatment (EUR-1008 is not currently commercially available) at their usual dose while undergoing Screening procedures and assessments. Eligible patients were entered into the study and underwent randomization to treatment sequence (EUR-1008 → placebo, or placebo → EUR-1008).
- Wash-out Period (2 days): Patients received no PEP treatment during the Wash-out Period.
- Dose-Titration/Stabilization Period (6 to 9 days): Open-label period during which patients were titrated to an appropriate dose of EUR-1008, beginning at a similar dose (based on lipase units) as their usual treatment. Titration to “appropriate dose” was performed by the investigator, who individually adjusted the patient’s dose to control the patient’s clinical symptoms of EPI. The appropriate dose determined during this period was the dose taken by the patient in the DB Treatment Period and in the two OL Normalization Periods.
- Randomization Treatment Period 1 (6 to 7 days): Patients were randomized to receive either DB placebo or EUR-1008 during this period (the dose of EUR-1008 was determined during the Dose-Titration/Stabilization Period). The first 72-hour stool collection for CFA was collected on Days 3 to 5 (or 6, if needed) of this period.
- Open-Label Normalization Period 1 (5 to 14 days): Patients were treated with a stable dose of EUR-1008 (there was no wash-out period after the first Treatment Period).
- Cross-Over Treatment Period 2 (6 to 7 days): Patients received the alternate DB treatment during this Treatment Period (patients who received placebo in Treatment Period 1 received EUR-1008 during Treatment Period 2, patients who received EUR-1008 during Treatment Period 1 received placebo during Treatment Period 2). The second 72-hour stool collection for CFA was collected on Days 3 to 5 (or 6) of this period.
- Open-Label Normalization Period 2 (7 days): Patients were treated with a stable dose of EUR-1008. End-of-study assessments were conducted at the end of this period.

The study design is represented graphically in the following figure (electronically copied and reproduced from the Applicant’s submission):

Figure 1: Study 1008M, Overall Study Design



The results of the study show that 34 patients were enrolled in the study, and 33 patients were randomized (one patient withdrew consent after entry into the study, but prior to randomization). Thirty-two patients completed both DB treatment periods (efficacy analysis population) and 31 patients completed the study. One patient withdrew consent and another patient was withdrawn by the Investigator (inclusion/exclusion criteria protocol violation, patient had undergone colectomy) prior to study completion. There were no withdrawals for Adverse Events (AEs).

Fifteen (15) patients were randomized to treatment sequence 1 (placebo → EUR-1008) and 17 patients to treatment sequence 2 (EUR-1008 → placebo). Compliance with study medication was high (>95%) overall and during both DB treatment periods.

The mean age of study entrants (n=34) was 15.5 years (range 7 to 23 years), and 65% of patients were 16 years of age or younger. Fifty percent (50%) of patients were male (consistent with the autosomal recessive inheritance of CF), and 94% were Caucasian, which is consistent with the racial/ethnic prevalence of the disease. Most patients were on

multiple medications at study entry, which were continued during the study, most commonly multivitamins and respiratory agents (e.g., dornase alfa or beta-adrenergic agonists). Proton pump inhibitors (PPIs) or other medications that alter gastric pH were specifically excluded from use during the study, but the majority of patients (56%) reported taking these medications prior to study entry, and discontinued their use during the study.

The primary efficacy endpoint showed that mean CFA for patients during placebo treatment was 63%, and during EUR-1008 treatment was 88%. The mean difference in CFA on EUR-1008 as compared to placebo was 25%, which was a statistically significant difference ($p < 0.001$; 95% CI [-32, -19]). These results were confirmed by the FDA Statistical Reviewer. The results are summarized in the following table (electronically copied and reproduced from the Applicant's submission).

Table 2: ANOVA Model Results of CFA (%)

	EUR-1008 (N=32)	Placebo (N=31)
Mean (SEM)	88.3 (1.4)	62.7 (3.4)
SD	7.9	19.1
Median	89.8	65.8
Min, Max	62.9, 98.7	28.7, 95.5
LS means (SEM)	88.3 (2.6)	62.8 (2.66)
Difference between EUR-1008 and Placebo		-25.5
95% CI		(-31.7, -19.3)
<i>P</i> value		<0.001

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

A subgroup analysis was performed by the Clinical and Statistical Reviewers for change in CFA by placebo-treatment (no-treatment) CFA, where patients were evaluated by the no-treatment CFA subgroups of severely-affected (CFA $\leq 40\%$), moderately-affected (>40 and $\leq 80\%$), and mildly-affected ($>80\%$). The widely accepted (in the medical literature) definition for severe steatorrhea is a no-treatment CFA of $\leq 40\%$; there are no generally accepted definitions for moderately- and mildly-affected patients, and these cut-points were arbitrarily selected. In severely-affected patients, an increase in CFA of $\geq 30\%$ is accepted as being clinically meaningful; however, for the moderately- and mildly-affected patients, there is no generally accepted change in CFA that is considered as being clinically meaningful.

The subgroup results showed that for the severely-affected patients ($n=5$) the mean CFA during placebo treatment was 35%, mean CFA during EUR-1008 treatment was 82%, and the mean difference on EUR-1008 as compared to placebo was 47%. This difference between the two treatment periods is clinically meaningful and statistically significant ($p=0.001$), although the number of patients in this subgroup is small. For the moderately-affected patients, the mean CFA during placebo treatment was 62%, mean CFA during EUR-1008 treatment was 88%, and the mean difference on EUR-1008 as compared to placebo was 26% ($p < 0.001$). For the mildly-affected patients, the mean CFA during placebo treatment was 93%, mean CFA during EUR-1008 treatment was 94%, and the mean difference on EUR-1008 as compared to placebo was 1% ($p=0.722$). The subgroup

results by placebo-treatment CFA are summarized in the following table (electronically copied and reproduced from Dr. Cooner's review):

Table 3: ANOVA Model Results of CFA (%) Stratified by Placebo (Pbo) CFA

	EUR-1008	Placebo
Placebo CFA < 40	(N=5)	(N=5)
Mean (SEM)	81.9 (5.4)	35.1 (1.9)
SD	12	4.212
Median	83.7	37.73
Min, Max	62.9, 93.2	28.7, 38.3
LS means (SEM)	81.8 (4.4)	35.0 (4.4)
Difference btw EUR-1008 and Pbo		-46.8
95% CI		(-62.4 -31.2)
<i>P</i> value		0.001
Placebo CFA in [40, 80]	(N=21)	(N=21)
Mean (SEM)	88.3 (1.5)	62.2 (2.4)
SD	6.7	11.2
Median	88.8	65.8
Min, Max	67.8, 97.8	40.5, 79.1
LS means (SEM)	88.0 (2.1)	61.9 (2.1)
Difference btw EUR-1008 and Pbo		-26.1
95% CI		(-31.4 -20.8)
<i>P</i> value		<0.001
Placebo CFA > 80	(N=5)	(N=5)
Mean (SEM)	93.6 (2.0)	92.8 (1.3)
SD	4.4	2.8
Median	94.0	93.2
Min, Max	86.5, 98.7	88.2, 95.5
LS means (SEM)	93.7 (1.8)	92.9 (1.8)
Difference btw EUR-1008 and Pbo		-0.8
95% CI		(-6.9, 5.2)
<i>P</i> value		0.722

The results were also analyzed by the Clinical and Statistical Reviewers to assess the effect of treatment sequence on the results of the primary endpoint. The Clinical Reviewer also performed assessments by demographic factors, including age and gender; there were too few non-Caucasian patients to assess the results by race. No effects on the overall results of the study were seen by either Reviewer for any of these factors.

Overall, the results for the primary endpoint show that treatment effect tends to have a linear relationship with the no-treatment (placebo) condition of the patient. That is, patients who were more severely affected (lower no-treatment CFA), tended to have higher increases in CFA on EUR-1008 treatment. This result is consistent with the previous experience with the PEPs, since patients with a lower CFA on no-treatment have a higher capacity to respond to treatment. No other factors were identified in this study that appeared to have an effect on response, including treatment sequence, age, or gender. Limitations in this study include the small numbers of patients included in the study, and the small number of patients in the severely-affected (n=5) subgroup.

Despite the limitations of the study, the results demonstrate a statistically significant and clinically meaningful benefit to treatment with EUR-1008 in patients with EPI due to CF, ages 7 to 23 years, and support the approval of EUR-1008 for the treatment of steatorrhea due to EPI.

2. Study EUR-1009-M

The Pediatric Study EUR-1009-M was a multi-center, non-randomized, open-label, uncontrolled, single-arm, safety and efficacy study of EUR-1008 administered to 19 infants and children with CF and EPI, ages one to six years. The objectives of the study were to describe the short-term (approximately 14 days) safety and efficacy of EUR-1008. The primary endpoint was the percentage of “responders” after one and two weeks of treatment with EUR-1008. Responders were defined as patients without steatorrhea (<30% fecal fat content) *and* without signs and symptoms of malabsorption (e.g., normal stool consistency) at Days 11 and 18 after 7 and 14 days, respectively, of EUR-1008 treatment compared with Screening (while on usual PEP treatment).

There was no PEP wash-out period during the study, and patients were maintained on OL PEP treatment throughout the duration of the study. Patients were transitioned from their usual commercially available PEP treatment at study entry to treatment with EUR-1008 in a dose range that complied with CFF recommendations. Doses of EUR-1008 were not to exceed 2,500 lipase units/kg/meal or 10,000 lipase units/kg/day. Given the young ages of the patients, most patients received EUR-1008 5,000 U capsules that were opened and mixed into soft foods for oral administration.

The study design consisted of the following periods:

- Screening Period (Days 1 to 4): Patients were continued on their usual commercially available PEP treatment at their usual dose while undergoing Screening procedures and assessments. Eligible patients were entered into the study. A Screening stool sample (on usual treatment) for spot fecal fat testing was collected during this period.
- Dose-Stabilization Period (Days 5 to 11): Patients were transitioned to EUR-1008 beginning at a similar dose (based on lipase units) as their usual treatment. Titration to “appropriate dose” was performed by the investigator, who individually adjusted the patient’s dose to control symptoms. The appropriate dose determined during this period was the dose taken by the patient in the Treatment Period (7 days). The first on-treatment (with EUR-1008) stool sample for spot fecal fat testing was collected on Day 11.
- Treatment Period (Days 12 to 19): Patients were treated with EUR-1008 at the dose determined during the Dose-Stabilization Period. The second on-treatment (with EUR-1008) stool sample for spot fecal fat testing was collected on Day 18.

The results of the study show that 19 patients were enrolled, and all 19 patients completed the study; however, one patient (104902) was missing an End-of-Study result. The mean age of patients enrolled was 3.9 years (range 1.2 to 6.4 years). By age subgroup, there

were five patients 1 to 2 years of age (inclusive of patients from 1.0 up to 2.9 years of age), ten patients 3 to 4 years of age (3.0 to 4.9 years inclusive), and four patients 5 to 6 years of age (5.0 to 6.9 years inclusive). Twelve patients (63%) were males, and 100% were Caucasian (CF has a higher prevalence in Caucasians, and a predominance of Caucasians in the study reflects the prevalence of the disease in the US population). All patients were administered concomitant medications during the study, most commonly multivitamins and respiratory agents, such as beta-adrenergic agonists and dornase alfa.

The primary efficacy endpoint showed that the percentage of “responders” at Screening (usual treatment) was ten patients (53%), at Visit 3 (at the end of the Dose-Stabilization Period) was 13 patients (68%), and at the End-of-Study visit (at the end of the Treatment Period) was 11 patients (58%). Four patients (21%) were classified as responders at each visit during the study, and two patients were non-responders at all visits during the study. For the ten patients who were classified as responders at Screening, nine of these patients were classified as responders during at least one of the two study visits after transition to EUR-1008 treatment. For the nine patients who were non-responders at Screening (on usual treatment), seven of these patients were classified as responders at Visit 3 or the End-of-Study visit (or both) while on EUR-1008 treatment.

The Medical Reviewer additionally analyzed the results of the fecal fat testing alone, without the subjective assessment of response by signs and symptoms of malabsorption. The results show that for the cut-point of fecal fat <30% selected by the Applicant as defining patients without steatorrhea, at Screening 14 of 19 patients had a fecal fat <30%, at Visit 3 13 of 19 patients had a fecal fat <30%, and at End-of-Study 13 of 18 patients had a fecal fat <30%, and throughout the study, 16 of 19 patients had a fecal fat <30% at one or more study visits. Thus, the majority of patients were without steatorrhea during the study, whether on their usual PEP treatment or after transition to treatment with EUR-1008.

Overall, these results are consistent with most patients in the study showing response to PEP treatment whether on their usual treatment at Screening or after transition to EUR-1008. Thus, these results are supportive of the effectiveness of EUR-1008 in pediatric patients with CF and EPI, ages one to six years of age. The results would allow for the extrapolation of the benefit of treatment seen with EUR-1008 (by change in CFA) obtained in the Pivotal Study EUR-1008-M, and would allow for labeling of the EUR-1008 product in patients with EPI from the ages of one year through adulthood.

3. Efficacy Conclusions

The efficacy findings from the two short-term efficacy and safety studies conducted with EUR-1008 show that:

- The treatment of pediatric and adult patients with CF and EPI, ages seven years and older, with EUR-1008 results in a statistically significant and clinically meaningful benefit to patients, as shown by mean increases in CFA during EUR-1008 treatment as compared to placebo treatment. Subgroup analysis showed that severely-affected patients (patients with CFA less than 40% on placebo treatment) had the greatest increases in CFA on EUR-1008 treatment. These results are consistent with results

seen with other PEPs, and are supportive of the labeling of EUR-1008 for the treatment of steatorrhea in patients with EPI due to CF and other causes, ages seven years and older.

- The treatment of infants and children with CF and EPI, ages one to six years, with EUR-1008 showed that the majority of patients were able to maintain a response to PEP treatment after transition from their usual commercially-available PEP treatment to EUR-1008. Response was assessed by spot fecal fat testing (fecal fat <30%) and an absence of symptoms of malabsorption (e.g., normal stool consistency). These results are supportive of the effectiveness of EUR-1008 in pediatric patients, ages one to six years. These results additionally support the extrapolation of the benefit of treatment seen with EUR-1008 (by change in CFA) obtained in the Pivotal Study EUR-1008-M, and would allow for labeling of the EUR-1008 product in patients with EPI from the ages of one year through adulthood.
- Infants younger than one year of age were not studied in the clinical development program for EUR-1008, and the Applicant has requested a deferral for conducting a study in these children until the post-marketing period.

Overall, these efficacy findings support the approval and labeling of EUR-1008 for the treatment of steatorrhea due to EPI from CF or other causes, in infants, pediatric, and adult patients, ages one year and older.

C. Safety Results

1. Background

Porcine-derived PEPs have been in clinical use since prior to 1938, and there is extensive clinical experience with these products in human patients. This long-term safety experience has demonstrated that the PEPs are relatively safe, and the PEPs' Adverse Event (AE) profile has been well described in the clinical literature. The clinical benefits of PEP treatment in some populations have also been established, such as pediatric patients with CF, who have been shown to do better clinically over the long-term with PEP administration (i.e., gain weight, maintain growth, and have fewer disease complications).

In consideration of this long and extensive safety experience with the PEPs, the Guidance assessed that it is not necessary to conduct long-term safety evaluations of the PEPs in support of the PEP NDAs; however, short-term safety evaluation is required during the clinical efficacy studies. Since PEPs act locally in the Gastrointestinal (GI) tract and are not absorbed, the Guidance further recommended that the safety variables assessed should focus predominantly on the monitoring of clinical signs and symptoms (i.e., AEs) during these clinical trials.

One exception to the relative safety of the PEPs is the association of fibrosing colonopathy with PEP use. Fibrosing colonopathy associated with PEP use is rare, and most of the cases of fibrosing colonopathy have been reported in younger children with CF. Although

the etiology has not been completely elucidated, fibrosing colonopathy is thought to be related to high or inappropriate dosing of PEPs, or may result from excipients or the delayed release of enzymes in the colon with treatment with the delayed-release PEP formulations. Thus, the Cystic Fibrosis Foundation (CFF) in conjunction with the FDA have recommended that PEP doses not exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal (FitzSimmons et al., 1997³; Borowitz et al., 2002⁴). Since publication of these recommendations, cases of fibrosing colonopathy have been reported only sporadically, and are unlikely to be reported during the relatively small clinical trials conducted in support of the PEP NDAs. Thus, continued monitoring for fibrosing colonopathy associated with PEP use is likely to best be performed through global safety surveillance.

Consistent with the Guidance, the safety evaluations performed for the EUR-1008 clinical development program focused predominantly on the monitoring of clinical signs and symptoms (i.e., AE assessments) during the short-term clinical efficacy and safety studies conducted with EUR-1008, and no long-term safety studies were performed.

2. Safety Review

The safety information submitted in this NDA submission includes an Integrated Summary of Safety (ISS), and safety information from three individual clinical studies conducted with EUR-1008 (EUR-1008-M, EUR-1009-M, and PR-001). The most important safety information available for review in the NDA submission was the safety data obtained from the DB study EUR-1008-M.

The 120-Safety Update was also submitted during the review cycle (dated 16-May-2008). The Safety Update contained no new safety reports, and only limited new information since EUR-1008 is not currently a commercially marketed product, and there was only one ongoing study (another BA study, PR-002) during the review cycle. This one ongoing clinical study had no safety data available as of the cut-off date for the Safety Update.

3. Results

a) Exposure

The total patient exposure included in the safety evaluation of EUR-1008 was 64 patients from three clinical trials. Exposure included:

- Single-dose 75,000 U lipase (~1,100 U/kg) administration to 11 adult patients with CP in the BA study;
- Multiple-dose (5-times a day for 20 to 35 days) administration to pediatric and adult patients with CF, ages 7 years through adults, in Study EUR-1008-M, including:

³ FitzSimmons SC, Burkhart GA, Borowitz D, Grand RJ, Hammerstrom T, Durie PR, Lloyd-Still JD, Lowenfels AB. High-dose pancreatic enzyme supplements and fibrosing colonopathy in children with Cystic Fibrosis. *N Engl J Med* 1997;336:1283-1289.

⁴ Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with Cystic Fibrosis. *J Pediatr Gastroenterol and Nutr* 2002;35(3):246-259.

- Ages 7 to 12 years: 8 patients
 - Ages >12 to <16 years: 10 patients
 - Ages \geq 16 years: 16 patients (9 patients were \geq 18 years); and
- Multiple-dose (5-times a day for 14 days) administration to pediatric patients with CF, ages 1 to 6 years, in Study EUR-1009-M, including:
 - Ages 1 to 2 years: 5 patients
 - Ages 3 to 4 years: 10 patients
 - Ages 5 to 6 years: 4 patients

Patients included in the safety analysis are summarized in the following table:

Table 4: EUR-1008 Exposure, Safety Population

Study Description	Safety Population (n)	Demographics	EUR-1008 Exposure
EUR-1008-M Randomized, DB, PC study in patients with CF	34	17 males, 17 females Ages 7-23 yrs (mean 15.5 yrs) 32 Caucasian (94%)	5 doses/day (3 meals, 2 snacks) X 20-35 days. Not to exceed 2,500 U lipase/kg/meal ($\frac{1}{2}$ dose with snack) or 10,000 U lipase/kg/day
EUR-1009-M Non-randomized, uncontrolled, OL study in patients with CF	19	12 males (63%), 7 females (36%) Ages 1-6 yrs (mean 3.9 yrs) 100% Caucasian	5 doses/day (3 meals, 2 snacks) X 14 days. Not to exceed 2,500 U lipase/kg/meal ($\frac{1}{2}$ dose with snack) or 10,000 U lipase/kg/day
OL, single-dose, cross-over (fed vs. fed + EUR-1008) BA study in adult patients with CP	11	6 males, 5 females Ages ~20-67 yrs (mean ~52 yrs) Weight 51-103 kg (mean 68 kg) 9 Caucasian (82%)	Single-dose 75,000 U lipase (~1,100 U/kg)

b) Safety Findings

The AE profile of EUR-1008 as described in the individual studies was consistent with the currently described AE profile of PEPs in the medical literature. In general, AEs tended to reflect underlying disease, and were most commonly reported in the gastrointestinal (GI) and respiratory systems. There were no new or noteworthy AEs noted during the safety review.

In the EUR-1008 clinical development program there were no deaths, and no patient discontinued treatment with EUR-1008 during any of the clinical studies due to an AE. Three Serious Adverse Events (SAEs) were reported, two during EUR-1008-M and one during EUR-1009-M, including lung infection, hemoptysis, and upper respiratory tract infection, all of which were attributed to underlying disease and were assessed as unlikely to be related to study drug by the investigators. No cases of fibrosing colonopathy were reported, which is not unexpected given the rarity of fibrosing colonopathy and the small size of the safety population.

Review of the safety information in the DB, placebo-controlled study EUR-1008-M showed that the most commonly reported AEs were in the GI and respiratory systems, which is consistent with patients in this study having EPI due to CF. By preferred term, the

most commonly reported AEs were abdominal pain (reported by 44% of patients), flatulence (27%), and headache and abdominal distension (24% each). The majority of AEs were mild to moderate in severity. Due to the study design, EUR-1008 was administered to patients for a longer period of time than placebo (a mean of 30 days on EUR-1008 vs. 6 days on placebo), and not unexpectedly, more AEs were reported during EUR-1008 treatment; however, the types of AEs during both treatments were similar.

A similar AE profile was reported in the OL, uncontrolled study EUR-1009-M, with the majority of AEs being reported in the GI and respiratory systems. The most commonly reported AEs by preferred term were abdominal pain (26%) and steatorrhea (16%). Thus by the safety assessments collected in the EUR-1008 clinical development program, younger children appear to have a similar safety profile with EUR-1008 as do older children and adults, and most of the AEs appear to be disease related.

A total of six AEs were reported during the BA study, where EUR-1008 was administered as a single-dose. These AEs were: sore throat, oral ulceration, thrush, elevated liver enzymes (which resolved), elevated glucose (in a patient with diabetes mellitus), and allergic reaction to peanuts. These AEs were not attributed as being due to study drug by the investigators.

Thus overall, the AE profile of EUR-1008 is consistent with the AE profile of the PEPs as described in the medical literature, and no new or notable safety signals were identified.

D. Clinical Conclusions and Recommendations

The Clinical and Statistical Reviewers concluded that this NDA submission provides evidence of short-term efficacy for EUR-1008, and the Clinical Reviewer found that the safety profile of EUR-1008 is acceptable for treatment of this patient population. This Reviewer is in agreement with the Clinical and Statistical Reviewers that the clinical efficacy and safety findings from the EUR-1008 clinical development program support the approval and labeling of EUR-1008 for the treatment of steatorrhea due to EPI from CF or other causes, in infants, pediatric, and adult patients, ages one year and older.

VI. Clinical Site Inspections

Site inspections of two clinical sites and the central laboratory were performed by the Division of Scientific Investigations (DSI) as part of the review of this NDA submission. These inspections were of the following sites, all of which participated in the pivotal study EUR-1008-M:

- Site 105, Investigator Steven Boas, M.D., Glenview, IL.
- Site 103, David Schaeffer, M.D., Jacksonville, FL.
- Mayo Central Laboratory for Clinical Trials, Rochester, MN.

Important issues identified during the site inspections are summarized as follows (please see the Clinical Inspection Summary memorandum by Khairy Malek, M.D., for more detailed information on the results of the inspection).

For Dr. Boas' site (#105):

- Six patients were enrolled at this clinical site.
- The clinical site did not have the results for the primary endpoint (CFA) at the site, as these were done at Mayo Central Laboratory and the results were sent directly to the Applicant. Thus, the integrity of the data could not be verified.

For Dr. Schaeffer's site (#103):

- Four patients were enrolled at this clinical site.
- The clinical site did not have the results for the primary endpoint (CFA) at the site, as these were done at Mayo Central Laboratory and the results were sent directly to the Applicant. Thus, the integrity of the data could not be verified.

For Mayo Central Laboratory

- Inspection of the lab was limited to comparing the lab results for the primary endpoint obtained at the two clinical sites (103 and 105, above) with the data reported to the FDA.
- Review of the data showed that the data in the lab records were the same as what the data reported to the FDA. Thus, the data generated at the two clinical sites (103 and 105) were assessed as authentic and could be used in support of the NDA.

The overall assessment of the inspector from the inspection of the two clinical sites and the Mayo Central Laboratory was that the data are reliable and can be used in support of the NDA.

VII. Advisory Committee

An Advisory Committee was not convened for this application.

VIII. Trade Name Review

A review of the trade name "Zentase" was performed by the Division of Medication Errors Prevention (DMEP), Office of Surveillance and Epidemiology (OSE). Please see the completed consultation (by Deveonne Hamilton-Stokes) for more detailed information.

Important issues identified in the review of the proposed trade name are summarized as follows:

- DMEP considers the proposed trade name "Zentase" unacceptable (under 21 CFR 201.10(c)(5)) based on the orthographic similarity of the name and potential for confusion with two other marketed products Pentasa and Zantac.
- A letter was sent to the Applicant during the review cycle (dated 28-March-2008) notifying the Applicant that the proposed trade name "Zentase" was unacceptable and requesting submission of two alternative trade names. The Applicant subsequently proposed two new names "ZenPep" and "Zenase", which are under review.

Thus, at the time of this review, no trade name has yet been agreed upon with the Applicant.

IX. Pediatrics

EUR-1008 is intended for use by pediatric patients, the majority of whom have CF, and the Applicant intends to marketing EUR-1008 to pediatric patients should EUR-1008 receive NDA approval (EUR-1008 is not a currently marketed product). A recent CFF consensus statement⁴ recommends that all pediatric patients with CF be treated with PEPs as soon as CF is diagnosed, which would include the treatment of infants. Therefore, the evaluation of the safety and efficacy of EUR-1008 in children from infancy through adolescence in clinical trials is considered to be necessary for the adequate assessment of this product.

The overall EUR-1008 clinical development program has included pediatric patients in two short-term, safety and efficacy studies, which included patients ranging in age from one year through age 18 (and older). Exposure to EUR-1008 by age group is as follows: five infants 1 to 2 years of age (inclusive of patients from 1.0 up to 2.9 years of age), 22 children ages ≥ 3 to < 12 years, and 10 adolescents ages ≥ 12 to 16 years. Pediatric patients by age subgroups and by clinical study are summarized, as follows:

From Study EUR-1009-M

- Ages 1 to 2 years (inclusive of patients from 1.0 up to 2.9 years of age): 5 patients
- Ages 3 to 4 years (3.0 to 4.9 years inclusive): 10 patients
- Ages 5 to 6 years (5.0 to 6.9 years inclusive): 4 patients

From Study EUR-1008-M

- Ages 7 to ≤ 12 years: 8 patients
- Ages > 12 to < 16 years: 10 patients

No patients less than one year of age were evaluated in the EUR-1008 clinical development program. During the review cycle, the Applicant submitted a request for deferral from performing a pediatric study in children from one month through one year of age, which requested that they be allowed to perform this study in the post-approval period. The Applicant submitted a pediatric study plan for this study, which proposes to study four patients less than one year of age, with OL EUR-1008 in a study design similar to EUR-1009-M. The Applicant is requesting that this study be conducted in the post-marketing period as a Phase 4 commitment. The Division responded to the Applicants proposal with comments on the study design (e.g., increase the study size to six patients), but otherwise feels that the Applicant's request is reasonable.

Thus overall, pediatric patients from one to 18 years of age were represented in the EUR-1008 clinical program. The efficacy and safety of EUR-1008 was demonstrated in pediatric patients, and pediatric patients do not appear to be respond differently to EUR-1008 treatment than do adults. These results support the approval and labeling of EUR-1008 in patients with EPI due to CF and other causes, from ages one year through adulthood. The Applicant plans to study patients from one month through one year of age

in the post-approval period, and should EUR-1008 receive an Approval action in a subsequent review cycle, this study will likely be required of the Applicant as a post-marketing commitment.

X. Regulatory Conclusions

This Reviewer recommends that this NDA submission receive an Approvable action based on the large number of Drug Substance and Drug Product deficiencies noted by the CMC Review Team. The DS deficiencies, including deficiencies in the viral risk mitigation plan and in the manufacturing and control of the DS, have already been communicated to the manufacturer (Nordmark) in a letter (please see section II.A.1. of this review for a listing of the DS deficiencies). The DP deficiencies will be communicated by the Division to the Applicant (Eurand) in the Approvable (AE) letter. The wording to be included in the letter for the DP (CMC) deficiencies is as follows:

- 1) In section 3.2.P.3.5 (Submission dated July 31, 2007, Vol. 2, Section 3.2.P.3.5, pg 1) you indicate that process validation to the intended full commercial batch size for each manufacturing step will be completed prior to marketing. Please provide a summary of the anticipated validation program. Process validation should be performed on three consecutive, commercial scale drug product conformance lots. Please indicate when validation studies will be initiated and completed.
- 2) Provide detailed information regarding the chemistry, manufacturing and controls for the hypromellose phthalate used for enteric coating of the beads/small beads.
- 3) The stability data contained in your application are insufficient to support your requested dating period of (b) (4) for the drug product. ICH Q5C indicates that expiry dating of products in which the active components are proteins should be set using real time, real temperature stability data. Therefore, the data provided support an 18-month expiry.
- 4) Specify how long excursions up to 30°C are permitted, and provide data to support the excursions.
- 5) The Nordmark DMF # 7090 has been reviewed in support of NDA # 22-210 and found to contain deficiencies. A letter has been sent to Nordmark listing the deficiencies. Nordmark should address the deficiencies and update the DMF by directly submitting information to the DMF. Please notify us when Nordmark has submitted the requested information.
- 6) You have not submitted sufficient information in the NDA to evaluate your qualification program for the lipase olive oil substrate. Please provide qualification results for olive oil testing, and establish and justify specifications for critical olive oil components.

- 7) In regards to specifications for release and stability, acceptance criteria should be established based on manufacturing history, process capability and clinical experience. We have the following recommendations:
- a) Tighten acceptance criteria for the protease and amylase activity to reflect actual manufacturing capability, for both final and intermediate drug product.
 - b) Establish and justify release specifications for all drug product RP-HPLC peaks.
(b) (4)
Therefore, the current release specifications and stability specifications are not adequate.
 - c) Establish a release specification for Phthalic Acid (FPA) for the four drug product strengths, and provide a justification for the acceptance criteria chosen.
 - d) Revise the acceptance criteria for the Uniformity of Dosage Units so that they are the same for the clinical/stability lots and for the lots to be marketed. The proposed weight limit of (b) (4) of target fill weight is too broad to ensure consistent manufacturing of EUR-1008.
 - e) Establish and justify a specification for water content for drug product release and stability testing.
- 8) As part of the RP-HPLC assay validation, determine how much protein is retained on the column.
- 9) Develop a rigorous qualification program aimed at ensuring that the quality attributes of the internal reference standard are maintained when new internal reference standards are required and manufactured. The certificate of analysis for the RP-HPLC pancrelipase reference standard release testing only includes specifications for peak areas. We also recommend that an internal reference standard that reflects the commercial manufacturing process be used, in addition to the pancrelipase drug substance reference standard, in all release and stability testing.
- 10) The working standard certificate of analysis for batch # P13309305 has two different USP lipase specific activities depending on the USP reference standard used. Please develop and implement a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the reference standard.

There was one additional deficiency noted by the Clinical Pharmacology Reviewer regarding the validity of the data submitted for the *in vitro* stability study for the drug product when capsules are opened and the contents mixed with food. This deficiency is an approvability issue that will also need to be included in the AE letter. The wording to be included in the letter is as follows:

11) In an Information Request letter sent (February 15, 2008), we requested clarification of the *in vitro* stability data you provided in the July 31, 2007 submission (Module 3, Section 3.2.P.2.2 Drug Product, pp. 91-100). In your submission, you evaluated the *in vitro* stability of pancrelipase after the capsules were opened and the contents were mixed with various types of food. You provided the stability data for three batches of EUR-1008 capsules; however, we noted that the individual data for two of the three batches were identical. It is not clear to us whether these are the actual results, or whether there were errors in the dataset. Provide clarification on the stability data as part of your complete response.

The clinical data submitted in this NDA submission provide evidence of the short-term efficacy and safety of EUR-1008 for the treatment of steatorrhea in patients with EPI, ages one year through adulthood, and are supportive of the approval and labeling of EUR-1008 for this indication. Since EUR-1008 is likely to be used by pediatric patients as young as one month of age, should EUR-1008 be approved during a subsequent review cycle, then an additional pediatric study in this age group will be needed. The Applicant has submitted a pediatric deferral request, and has requested that this study be performed during the post-approval period. The Division feels this request is reasonable, and will likely require this study as a condition of Approval during a subsequent review cycle (i.e., as a post-marketing commitment). Other than the deferred pediatric study, no additional clinical studies are required of the Applicant at this time.

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/s/

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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-term 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) minitables (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)

Zentase is effective in controlling steatorrhea and malabsorption related symptoms.”

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, Burkhardt, 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 published³ (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

(b) (4)



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 (Mayo Central Laboratory for Clinical Trials, Rochester, MN) 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. [REDACTED] (b) (6) who was a clinical investigator for [REDACTED] (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, [REDACTED] (b) (4), 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	<i>Pivotal Study</i>	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
	<i>Supportive Study</i>	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	<i>Bioavailability Study</i>	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

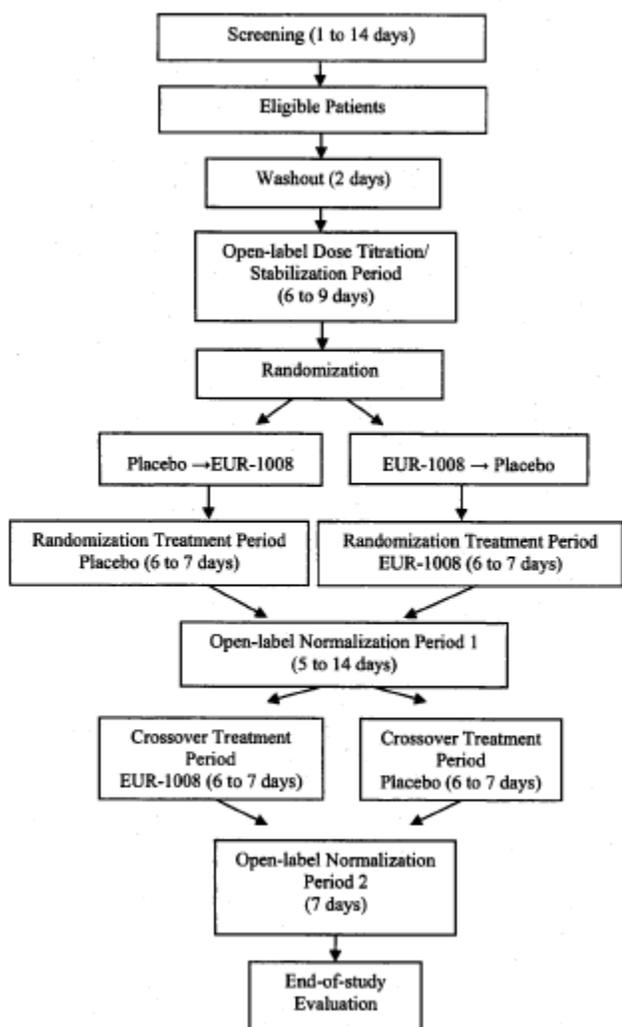
5.3.1 EUR-1008-M

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)
	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 ^l			Day 6 ^l	X
Study drug provided ^p			X		X	Daily		X	Daily	
Hospital diet record ^q						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 ⁿ	X	X	X	X	X	Daily	X	X	Daily	X
Dye administration ^o						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:

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

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):	15.5 (4.6)
	Range:	7-23
Age categories	7-11:	8 (24%)
	12-16:	14 (41%)
	≥17:	12 (35%)
Gender	Male:	17 (50%)
	Female:	17 (50%)
Ethnicity	Hispanic:	3 (9%)
	Non-Hispanic:	31 (91%)
Race	Caucasian:	32 (94%)
	Non-Caucasian:	2 (6%)
Duration (yrs) of CF diagnosis	Mean (SD):	14 (5.5)
	Range:	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 patient 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 in 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)
<i>P</i> 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	28.7	79.0	50.3
112803	32.8	83.7	50.9
102802	37.7	90.5	52.8
108801	37.9	93.2	55.3
105801	38.3	62.9	24.6
Mean	35	82	47
Median	38	84	51
Min, Max	29, 38	63, 93	25, 55

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	41	91	50
103802	42	91	50
109806	44	85	41
103801	49	93	43
116802	51	68	17
105805	55	82	27
105804	57	94	36
118803	61	87	26
109803	64	87	23
109805	65	82	16
105807	66	86	21
112805	68	97	29
101802	69	84	15
105806	69	95	26
115803	69	89	20
103803	70	83	13
118802	70	95	25
112804	71	91	20
115801	73	89	16
105803	74	87	13
106801	79	98	19
Mean	62	88	26
Median	66	89	23
Min, Max	41, 79	68, 98	13, 50

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	88	94	6
109804	92	94	1
115802	93	87	-7
112801	95	99	4
108802	.	95	.
116801	96	95	-0
Mean	93	94	1
Median	94	94	1
Min, Max	88, 96	87, 99	-7, 6

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	.	94.9	.
103804	28.7	79.0	50.3
112803	32.8	83.7	50.9
102802	37.7	90.5	52.8
109806	44.0	85.5	41.5
116802	50.7	67.8	17.1
118803	60.7	86.5	25.8
109803	64.1	87.2	23.1
101802	68.6	83.8	15.2
105806	68.7	94.8	26.0
115801	72.6	88.8	16.1
105803	73.9	86.8	12.8
109804	92.4	93.8	1.4
115802	93.2	86.5	-6.7
116801	95.5	95.1	-0.5
Mean	63	87	23
Median	66	87	20
Min, Max	29, 96	68, 95	-6.7, 53

Table 11: Sequence 2 Patients

Patient	Placebo	EUR-1008	Change in CFA
108801	37.9	93.2	55.3
105801	38.3	62.9	24.6
101804	40.5	90.7	50.1
103802	41.8	91.5	49.7
103801	49.3	92.7	43.4
105805	55.1	82.4	27.3
105804	57.3	93.8	36.5
109805	65.3	81.8	16.5
105807	65.8	86.4	20.6
112805	67.8	97.3	29.5
115803	69.4	89.1	19.7
103803	69.6	82.7	13.2
118802	69.8	95.0	25.2
112804	71.0	91.4	20.5
106801	79.1	97.8	18.7
101805	88.2	94.0	5.7
112801	94.5	98.7	4.2
Mean	62	90	27
Median	66	92	25
Min, Max	38, 95	63, 99	4.2, 55

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 A1 electronically 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)
<i>P</i> 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 $\geq 5\%$ 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)
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	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-1008, 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

¹X= Responder
²O = 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, after 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
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)

Zentase is effective in controlling steatorrhea and malabsorption related symptoms.”

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 pancreatotomy 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)
<i>P</i> 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 ($\geq 40\%$ 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

¹X= Responder
²O = 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/pharmacovigilance 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 postmarketing 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 (b) (4)
101805			
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 (b) (4)
101802			
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	37.7	90.5	52.8	11.3
105801	38.3	62.9	24.6	7.5
116802	50.7	67.8	17.1	8.6
118803	60.7	86.5	25.8	7.9
109805	65.3	81.8	16.5	10.9
103803	69.6	82.7	13.2	8.6
118802	69.8	95.0	25.2	7.9
109804	92.4	93.8	1.4	7.9
Mean	61	83	22	9
Median	63	85	21	8.6
Min, Max	38, 92	63, 95	1.4, 53	7.5, 11.3

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	32.8	83.7	50.9	14.8
103802	41.8	91.5	49.7	15.6
103801	49.3	92.7	43.4	16.1
105805	55.1	82.4	27.3	15.6
105804	57.3	93.8	36.5	16.6
109803	64.1	87.2	23.1	14.7
105807	65.8	86.4	20.6	14.6
101802	68.6	83.8	15.2	16.2
112804	71.0	91.4	20.5	13.7
115801	72.6	88.8	16.1	14.4
105803	73.9	86.8	12.8	14.7
106801	79.1	97.8	18.7	16.1
108802	94.9	94.9		14.1
Mean	64	89	28	15.2
Median	66	89	22	14.8
Min, Max	33, 95	82, 98	13, 51	13.7, 16.6

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	28.7	79.0	50.3	17.7
108801	37.9	93.2	55.3	18
101804	40.5	90.7	50.1	21.1
109806	44.0	85.5	41.5	22.3
112805	67.8	97.3	29.5	23.4
105806	68.7	94.8	26.0	17.5
115803	69.4	89.1	19.7	21.3
101805	88.2	94.0	5.7	20
115802	93.2	86.5	-6.7	22.1
112801	94.5	98.7	4.2	20.8
116801	95.5	95.1	-0.5	21.9
Mean	66	91	25	21
Median	69	93	26	21
Min, Max	29, 96	79, 99	-7, 55	17.5, 23.4

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	36, 94	69, 99	-1, 53

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 % (b) (4)
101901	SCREENING	0			
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			

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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/

Marjorie F. Dannis
6/15/2008 09:16:55 PM
MEDICAL OFFICER

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