CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-210

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA:	22-210
Proposed Brand Name:	Zenpep
Generic Name:	Pancrelipase
Dosage form and Strength:	Enteric-coated minitablets (or beads) in capsules; 5,000, 10,000, 15,000 and 20,000 lipase units/capsule
Route of administration:	Oral
Indication:	Replacement therapy in patients with partial or complete exocrine pancreatic insufficiency
Sponsor:	Eurand
Type of submission:	Resubmission
Clinical Division:	Division of Gastroenterology and Inborn Error Products (HFD-180)
OCP Division:	DCP III
Submission date:	01/09/09
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

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1. Executive Summary

1.1 Recommendations

NDA 22-210 for Zenpep has been reviewed by the Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP III). From the OCP standpoint, the NDA is acceptable provided that a mutual agreement on labeling language can be reached between the sponsor and Agency.

1.2 General Comments

The bioavailability study is currently not required for the NDA approval because many challenges in the study design and study conduct remain to be overcome before the study can be used reliably to assess the bioavailability of pancreatic enzyme products. As such, the sponsor's study results will not be reflected in the label.

1.3 labeling Comments

Labeling comments on page 5 need to be conveyed to the sponsor.

1.4 Phase IV Commitments: None

1.5 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

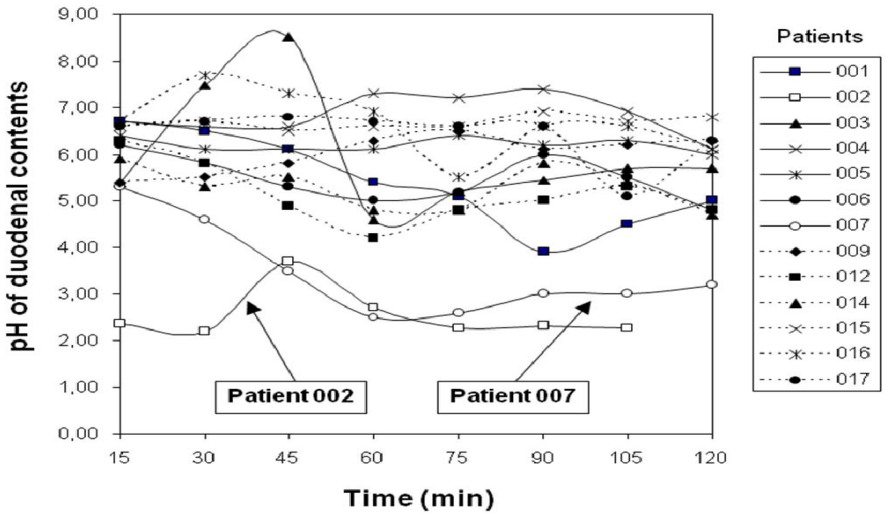
The original NDA 22-210 for Zenpep (Pancrelipase) capsules was submitted by Eurand on 12/14/07. In the Clinical Pharmacology and Biopharmaceutics section, two studies were submitted: 1) an *in vivo* intubation study (No. PR-001) and 2) an *in vitro* compatibility study to evaluate the stability of pancreatic enzymes following mixing of the Zenpep capsule contents with a variety of acidic foods. The above two studies were found not acceptable in the original review. The deficiencies related to the *in vivo* intubation study was considered not an approval issue. Therefore, the FDA's approvable letter dated 6/16/08 included only the comment related to the *in vitro* compatibility study.

Bioavailability study (Intubation Study)

After the submission of the original NDA on 12/14/07, the sponsor continued to enroll patients to study PR-001. The amended study report was submitted on 01/09/09, which includes data from a total of 17 patients, i.e., the original 11 patients and an additional 6 patients enrolled subsequently. Out of the 17 patients, six were excluded from the final analysis. These include 5 patients from the original study (2 patients were unable to tolerate the intubation and did not receive the medication, one did not meet the inclusion criteria, and two (#2 and #7; see Figure 1) had duodenal pH< 4.0 during the duodenal

aspiration period). One patient from the subsequent enrollment was excluded from the analysis due to extremely high baseline lipase value.

Figure 1: pH of Duodenal Contents After patients received Zenpep with Ensure Plus



The sponsor provided the results from 11 patients as shown in Table 1.

Table 1. Duodenal Samples: Lipase Dose Recovered (units) by Treatment Condition

Patient No.	Dose Recovered (units)		Bioavailability (%)
	Ensure Plus and EUR-1008	Ensure Plus only	
001	27480	20041	10.82
003	99900	50853	71.31
004	20318	336	29.05
005	52292	684	75.03
006	25534	4551	30.51
009	33822	19152	21.33
012	23867	3105	30.19
014	222371	227393	-7.30
015	43045	0	62.58
016	289836	306057	-23.58
017	63876	26315	54.61
Total, n	11	11	11
Mean	82031.0	59862.5	32.23
(SD)	(90340.93)	(104898.85)	(31.706)
Median	43045	19152	30.19
(IQR[3])	(74366.0)	(50169.0)	(51.76)
CI 95%	21339 - 142723	-10610 - 130334	10.93 – 53.53
Wilcoxon Signed-Rank Test	**p = 0.013**		

[1] The patient number 010 (outlier) is removed from the analysis.
IQR = Inter Quartile Range.
Source : Table 2.8, Statistical Analysis Report, Appendix 16.5

Reviewer's Comments:

1. Table 1 showed that Patient #14 and #16 had negative values in the recovery of lipase. It is noted that these two patients had very high endogenous lipase levels (227,393 and 306,057 units) after consuming the food alone (Ensure Plus only), which were about 3.5 to 4 times higher than the lipase dose administered (i.e., 75,000 units). The variability in assay results yielded negative values. These two subjects apparently had high endogenous lipase levels and should not have been included in the study.
2. Further inspection of the individual duodenal pH profiles revealed that Patients #1 and #6 had low duodenal pH (<4.0) during the food only study period (Table 2) which might impact the results.
3. Even in a patient with high duodenal pH's (>5.0), variable lipase levels over the sampling period was observed following Ensure plus only administration. It is uncertain that same endogenous lipase levels would occur in the two treatment periods (Ensure Plus with and without Zenpep), raising the question whether Ensure Plus only can serve as a reliable control for estimation of Zenpep bioavailability. (See Tables 2 & 3.)
4. Based on the data provided, the reliability of the study cannot be assured. As such, the study results will not be reflected in the label. However, as stated before, the bioavailability study is not required for the NDA approval.

Table 2: Duodenal Sample pH in Study PR-001 (Ensure Plus only)

		Time (min)						
Patient Number	15	30	45	60	75	90	105	120
001	5.7	5.0	3.9	3.3	1.9	2.1	1.9	2.3
002	2.2	2.4	2.1	2.6	3.2	2.7	2.5	6.4
003	6.1	5.5	6.4	5.6	5.0	4.2	4.0	4.4
004	6.4	6.5	6.6	6.8	6.5	6.8	5.6	4.8
005	6.3	6.0	6.1	5.9	5.8	5.6	5.8	5.3
006	5.9	5.5	5.0	4.3	4.3	3.0	2.4	3.4
007	6.3	6.5	6.4	5.4	5.0	2.9	2.8	4.1
009	5.5	2.9	5.1	6.0	6.3	6.5	6.5	6.8
010	6.4	5.7	5.1	4.1	3.5	3.3	3.5	3.6
011	6.6	5.8	5.5	6.9	4.5	4.3	4.4	4.2
Patient Number	15	30	45	60	75	90	105	120
012	6.6	7.1	6.4	6.4	6.5	6.7	6.0	6.3
014	6.1	5.7	5.5	5.8	4.3	6.6	4.9	4.1
015	6.8	6.7	6.8	6.9	6.7	6.9	6.7	6.7
016	6.9	6.8	6.9	7.4	7.9	7.0	6.4	7.2
017	5.7	5.5	5.9	5.0	5.2	4.7	6.4	4.8

Table 3: Lipase amount at various sampling times (Ensure Plus Only)

Listing 11 (Page 4 of 4) **Ensure Plus only:** Lipase amount (with PEG correction)											
Lipase amount (Units)											
Patient Number	Time (min)										
	Washout	Baseline	15	30	45	60	75	90	105	120	Final
001	6914	1775	10385	3183	2599	2310	1564	0	0	0	0
002	0	0	0	0	0	0	0	0	0	834	0
003	0	24198	9335	10889	11487	7917	5430	1708	2413	1674	437
004	0	0	0	0	0	0	0	336	0	0	0
005	0	865	0	0	532	0	0	0	152	0	823
006	5065	0	4551	0	0	0	0	0	0	0	0
007	2187	0	3851	6289	6774	6502	3481	3863	2841	2117	1851
009	0	0	0	0	0	0	804	2582	6401	9365	0
010	107635	132170	424485	218498	37677	30624	12470	4140	39815	13300	0
011	0	1368	60772	21666	15894	12983	4516	5387	150	6798	2550
012	0	0	1680	0	0	0	0	0	0	1425	0
014	12491	0	46717	32686	19973	35304	9268	28297	25356	29792	0
015	0	0	0	0	0	0	0	0	0	0	0
016	27902	51938	31941	14136	16317	23150	12671	87615	51173	69054	0
017	3120	445	7617	0	5309	0	2975	0	7418	2996	0

In Vitro Compatibility Study

The Agency's approvable letter dated 06/16/08 included a comment regarding the errors found in the *in vitro* stability study report as shown below.

"In an Information Request letter sent on 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 sponsor, however, found the errors before then and submitted the revised table on 6/9/08 in their response to other CMC information requests. The revised results are shown in Table 4.

Table 4. *In Vitro* Compatibility between Zenpep Capsule Contents and Several Types of Food: Recovery of Lipase 60 minutes after mixing

Batch Nos.	USP Dissolution Part 2 (pH 6.0 for 30 min)		
	P200550387	P200550348	P200550668[1]
Food Type	Mean (CV) % dissolved[2]		
Applesauce Mott's	100 (1.5)	94 (1.0)	92 (3.0)[2]
Applesauce Gerber	98 (1.5)	97 (1.6)	89 (1.2)
Bananas	99 (1.1)	91 (1.1)	89 (3.0)
Pear	99 (1.8)	99 (2.8)	98 (2.8);
Pudding Vanilla/Apples	102 (2.7)	96 (1.0)	91 (1.0)
Banana Pudding	102 (2.5)	95 (1.6)	91 (5.0)
Banana juice/yogurt	99 (0.6)	92 (1.3)	90 (1.4)
Mixed fruit juice/yogurt	96 (5.1)	96 (5.1)	94 (1.3)
Grated apple with sugar and lemon	92 (2.0)	92 (3.1)	88 (0.9)
Smashed banana with sugar and lemon	100 (2.2)	98 (1.5)	91 (5.3)
Range of the Means	92-102	92-102	88-94

1. Batch No. P200550668 was used for production of 5,000 units USP lot No. P200550785 used for Study PR-001 study and EUR-1009-M.
2. A mean of 6 readings per batch.

Reviewer's Comments:

1. Based on the sponsor's data, applesauce and pear had the lowest pH (3.5-4.0) and vanilla pudding alone had the highest pH (5.5-6.1). However, the *in vitro* results presented in Table 4 did not show a correlation between food pH and lipase recovery. The testing procedures might have contributed to the variability.
2. The above in vitro study involved mixing capsule contents with food which was let stand for 60 minutes. However, we will instruct patients to take it immediately after mixing.

2. Detailed Labeling Recommendations

(b) (4)

[redacted]

3. Appendices

3.1 Proposed Package Insert (02/05/09 version)

3.2 Study Synopsis (Addendum)

NDA 22-210 for Zenpep (Pancrelipase) MT Delay-Release Capsules

Appendix 1

Proposed Package Insert (02/05/09 Version)

25 pp withheld in full immed. after this page as (b)(4) Draft Labeling.

NDA 22-210 for Zenpep (Pancrelipase) MT Delay-Release Capsules

Appendix 2

Revised Study Synopsis (01/09/09)

3 SYNOPSIS

Name of Sponsor: Eurand S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*For regulatory use only*
Name of Finished Medicinal Product: EUR-1008 (pancrelipase [Zentase™])	**Volume:**	
Name of Active Ingredient: Pancrelipase	**Page:**	
Title of Study:	Study of the Gastrointestinal Bioavailability of a Novel Pancreatic Extract Product (EUR-1008) in Chronic Pancreatitis Patients with Exocrine Pancreatic Insufficiency (Addendum)	
Investigator:	Phillip Toskes, MD	
Study Site:	Shands Hospital, University of Florida	
Publications:	None	
Period of Study:	Date of Study Initiation: 6 September 2007 Date of Study Completion: 17 July 2008	
Phase of Development:	1	
Objective(s):	Efficacy Objectives: The objective of the study was to determine the bioavailability of lipase, chymotrypsin, and amylase from EUR-1008 in the duodenum under fed conditions after administration of a test meal (Ensure Plus®) in patients with chronic pancreatitis (CP) with severe exocrine pancreatic insufficiency (EPI). The study also determined whether CCK blood levels were affected following the administration of EUR-1008. Safety Objectives: The safety objectives were to determine the frequency, duration, and severity of treatment-emergent adverse events (AEs) and changes in clinical laboratory findings.	
Methods:	This study was an open-label, randomized, single center, single treatment, 2-period, crossover trial. The study consisted of a screening period and a 5- to 6-day hospitalization period with 2 separate gastroduodenal	

Name of Sponsor: Eurand S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*For regulatory use only*
Name of Finished Medicinal Product: EUR-1008 (pancrelipase [Zentase™])	**Volume:**	
Name of Active Ingredient: Pancrelipase	**Page:**	

perfusion procedures.

Patients signed an informed consent before discontinuing any exclusionary drugs or undergoing any study procedures. Patients were allowed to sign the informed consent at home; they signed an additional informed consent at the time of hospitalization. Exclusionary drugs (proton pump inhibitors, antacids and drugs capable of altering gastrointestinal motility) were discontinued 7 days prior to entering the General Clinical Research Center (GCRC).

Day 1: After presenting their original signed informed consent and signing an additional informed consent on the day of hospitalization, patients entered the GCRC at the Shands Hospital, University of Florida. The Principal Investigator (PI) evaluated the eligibility of the patient for the trial, and medical history, physical examination, and blood and urine samples were collected.

Day 2: Patients were randomized to receive either a test meal (Ensure Plus) alone or Ensure Plus with EUR-1008, according to a predetermined randomization scheme. The dose of EUR-1008 was 75,000 USP lipase units (3 capsules containing 20,000 units each plus 3 capsules containing 5,000 units each) per procedure. After placement of the duodenal tube, perfusion and aspiration were begun, and duodenal washout and baseline samples were collected at 30 minutes and 60 minutes after the start of perfusion. At 60 minutes after the start of perfusion (after the baseline sample was collected), perfusion and aspiration were halted for 20 minutes to allow the patient to drink the test meal (Ensure Plus with or without EUR-1008). After this 20-minute meal break, perfusion resumed. Five minutes later, aspiration also resumed, and

Name of Sponsor: Eurand S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*For regulatory use only*
Name of Finished Medicinal Product: EUR-1008 (pancrelipase [Zentase™])	**Volume:**	
Name of Active Ingredient: Pancrelipase	**Page:**	
	both perfusion and aspiration were performed continuously for 2 hours. Samples were collected at 15-minute intervals for 2 hours. After 2 hours, aspiration of gastric contents was performed for 15 minutes (or for a maximum of 30 minutes if the sample quantity was insufficient). Day 3: Washout day. An abbreviated physical exam was done on this day. Day 4: The same procedures followed on Day 2 were repeated. Patients who received Ensure Plus alone on Day 2 received Ensure Plus with EUR-1008 on Day 4 or vice versa. Day 5: Complete physical exam and blood and urine samples were collected. Patients were discharged. The bioavailability of EUR-1008 was estimated by calculating the difference between the amount of lipase released and recovered in the duodenum (lipase output) under fed conditions with and without EUR-1008.	
Number of Patients (planned and analyzed):	12 evaluable male or female adult patients were planned and 17 patients were enrolled, 15 of whom were treated and had post-treatment data collected. Three patients were excluded from the Efficacy Analysis Population because of protocol violations (1 patient who did not meet inclusion/exclusion criteria, and 2 patients who were unable to tolerate the Dreiling tube and thus could not receive study medication). A fourth patient was excluded from efficacy analyses as a statistical outlier. The Efficacy Analysis Population therefore included 13 patients. The Safety Population included the 15 patients who received study medication.	

Name of Sponsor: Eurand S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*For regulatory use only*
Name of Finished Medicinal Product: EUR-1008 (pancrelipase [Zentase™])	**Volume:**	
Name of Active Ingredient: Pancrelipase	**Page:**	
Diagnosis and Main Criteria for Inclusion:	Patients of either sex over the age of 18 with a documented history of CP with severe EPI and significant steatorrhea and a fecal elastase level below 100 mcg/g.	
Test Product, Dose, and Mode of Administration, Batch Number:	EUR-1008 was administered orally with 480 mL of Ensure Plus as a single fixed dose of 75,000 USP lipase units (the contents of 3 capsules of 5,000 USP lipase units plus the contents of 3 capsules of 20,000 USP lipase units) per procedure per patient. Batch Number: 20,000 USP lipase units: 058761C; 5,000 USP lipase units: 058755B	
Duration of Treatment:	One administration of test product	
Reference Therapy, Dose and Mode of Administration, Batch Number:	480 mL Ensure Plus™ alone, orally	
Criteria for Evaluation:	The primary efficacy endpoint (the bioavailability of lipase from EUR-1008) was estimated by comparing the recovery of lipase under the 2 treatment conditions (Ensure Plus alone and Ensure Plus with EUR-1008) after administration of the test meal. Secondary efficacy endpoints included the bioavailability of chymotrypsin and amylase estimated by comparing their recovery under the 2 treatment conditions (Ensure Plus alone and Ensure Plus with EUR-1008) after administration of the test meal; the measurement of cholecystokinin (CCK) levels in blood; and the measurement of duodenal and gastric pH. Safety was evaluated in terms of the occurrence of adverse events (AEs) and changes in clinical laboratory parameters, physical examination findings, and vital sign	

Name of Sponsor: Eurand S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*For regulatory use only*
Name of Finished Medicinal Product: EUR-1008 (pancrelipase [Zentase™])	**Volume:**	
Name of Active Ingredient: Pancrelipase	**Page:**	
	measurements.	
Statistical Methods	Descriptive statistics of the various parameters and the corresponding lower and upper 95% confidence intervals (CI) were computed. For continuous variables, descriptive statistics for each treatment sequence included mean, standard deviation, median, lower and upper 95% CI, minimum, maximum, and number of non-missing observations. The descriptive statistics for dichotomous or categorical variables were numbers and percentages of each of the scores or categories for each treatment. The bioavailability of EUR-1008 was estimated by comparing the recovery of lipase, amylase, and chymotrypsin in the 2 treatment conditions (Ensure Plus alone and Ensure Plus with EUR-1008) after administration of the test meal. Statistical significance was evaluated by means of a paired samples t-test. Because 2 different pH subpopulations of patients were identified in this study, efficacy results and tabulations of data are also presented for a subpopulation (N = 11) of patients whose gastric pH was not excessively acid. Two patients whose pH values indicated acid hypersecretion were removed from this pH Subpopulation. All AEs were listed, and the frequency of treatment-emergent AEs was tabulated by system organ class and preferred term. All laboratory data were listed and analyzed using the appropriate statistical methods.	

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

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/s/

TIEN MIEN CHEN
08/12/2009

SUE CHIH H LEE
08/17/2009

Clinical Pharmacology Review

NDA:	22-210
Brand Name:	Zentase
Generic Name:	Pancrelipase
Dosage form and Strength:	Enteric-coated minitablets (or beads) in capsules; 5,000, 10,000, 15,000 and 20,000 lipase units/capsule
Route of administration:	Oral
Proposed Indication:	Pancreatic enzyme replacement therapy for the treatment of malnutrition associated with Exocrine Pancreatic Insufficiency
Sponsor:	Eurand Inc.
Type of submission:	Original Submission [505(b)(2)]
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCP Division:	DCP III
Priority:	Priority
Submission date:	12/14/07, 02/12/08, 03/07/08
PDUFA Goal date:	06/17/08
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

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1. Executive Summary

1.1 Recommendations

NDA 22-210 for Zentase (Pancrelipase) capsules has been reviewed by the Office of Clinical Pharmacology/ Division of Clinical Pharmacology III (OCP/DCP III). OCP/DCP 3 is of the opinion that the clinical pharmacology section of this NDA is not acceptable. The comments below should be conveyed to the Medical Officer of HFD-180 and the sponsor.

1.2 Comments

1. The NDA is not acceptable from a Clinpharm standpoint for the following reasons:
   A. Regarding *in vivo* intubation study (PR-001),
      i. 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 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.
      ii. 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.
      iii. The number of patients is too small (N=8) in view of the high variability observed in the study.
   B. Regarding the *in vitro* stability data for three batches of Zentase 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.

2. 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.

1.3 Phase IV Commitments: N/A

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Eurand has developed Zentase (pancrelipase) which has not been commercially available in any countries. Zentase is reported as a new porcine-derived pancreatic enzyme replacement product for the treatment of malnutrition in patients of chronic pancreatitis (CP) with exocrine pancreatic insufficiency (EPI). They are enteric coated (EC) minitablets (or beads) in capsule formulation containing no overfill in each capsule.

Eurand submitted NDA 22-210 for Zentase on 12/14/07 under 505(5)(2), the subject of this Clinpharm review. To support this NDA, the sponsor conducted, an *in vivo* intubation (bioavailability; BA) study PR-001, an *in vitro* stability study of Zentase content sprinkled on food, and 2 clinical studies (EUR-1008-M and EUR-1009-M) as shown in Table 1.

Table 1. Clinical and *In Vitro* studies Submitted

Study No.	**No. of Patient Enrolled**	**Study Design[1]**	**Primary Endpoint or Analysis[1]**
PR-001	11 (20-67 yrs old)	R, OP, ST, 2x2	To determine the BA of Zentase in Duodenum in CP patients with EPI.
***In Vitro* Stability Study**	-----	---------	To assess the stability of Zentase content when mixed with food
EUR-1008-M (Pivotal Phase 3)	34 (8-23 yrs old)	R, DB, PC, 2x2, Multicenter	To compare the CFA for Zentase and Pbo in CF patients with EPI
EUR-1009-M (Supportive Phase 3)	19 (1-6 yrs old)	OP, non-R, ST, MD, Multicenter	To compare the responder rate & fecal fat excretion in CF patients with EPI for Zentase and Baseline (previous PEP administration)

[1]. R= randomized; DB= double blind; PC= placebo controlled; CFA= coefficient of fat absorption; Pbo= placebo; OL= open label; ST= single treatment; MD= multiple doe; CP= chronic pancreatitis; EPI= exocrine pancreatic insufficiency; BA= bioavailability.

I. In Vivo Intubation study: (PR-001)

The *in vivo* intubation study was a randomized, open-label, 2x2 crossover study to evaluate the bioavailability (BA) of Zentase in patients of CP with exocrine pancrelipase insufficiency (EPI) in gastric and duodenal aspirates under fed conditions.

The BA data of all 8 patients who completed the *in vivo* intubation/BA study and were considered evaluable "per protocol" were analyzed and presented in Table 2 below. Mean BA was reported to be 21.6% with a large intersubject variation ranging from -51.9% to 71.4%.

Patient Nos. 2 and 7 had lower duodenal pH values (<4.0). Lower BA found in these 2 patients could be due partly to a lower duodenal pH values since the Zentase is designed to release lipase at pH >5.0. Therefore, a separate analysis was conducted by excluding data from these 2 patients. Mean BA for rest of 6 patients was found to be 33.7% with a smaller intersubject variation ranging from 10.8% to 71.4%.

Table 2. Mean Bioavailability Obtained from Study PR-001

Bioavailability Study	**Mean (± SD) Recovery (units)**		**BA (%)**
	Zentase + Food	**Food only**	
N=8 (Per protocol)	32,418 (± 32,229) (0-99,900)*	16,521 (± 18,779) (336-50,853)	21.6 (±38.5)
N=6 (normal pH) **(excluding patient #s 2 &7)**	43,224 (± 29,894) (0-99,900)	15,936 (± 19,245) (336-50,853)	33.7 (±24.1)

*. Range.

Reviewer's Comment:

The above *in vivo* intubation (BA) study is not acceptable as explained in Section 1.2.

II. In Vitro Stability of Zentase Content:

The *in vitro* stability study was conducted to evaluate the influence of the contact of different common types of baby foods, either ready or to be prepared, on "gastroresistance" of Zentase EC capsules. This study used the contents of 5,000 units USP capsules since this strength is

specifically intended for administration in infants and young children. The results of *in vitro* stability test are shown below:

Table 3. *In Vitro* Stability Study for Zentase Content when Mixed with 10 Types of Food for 60 min

	USP Dissolution Test Part 2 (pH 6.0 for 30 min)		
	Mean (CV) % dissolved[1]		
Batch No.	P200550387	P200550348	P200550668[2]
Range of the Means[3]	92-102	92-102	88-94

1. Six tests per batch were performed for each of three batches.

2. The batch No. P200550668 was used for production of 5,000 units USP lot No. P200550785 used for 3 studies, PR-001, EUR-1008-M, and EUR-1009-M.

3. Range of 10 means from 10 different types of food tested for each batch.

Reviewer's Comment:
The individual data of two out of three Zentase batches were identical for *In vitro* stability study. Information request for clarification was made but the sponsor has not responded to this request.

III. Biopharmaceutics:

The commercial Zentase product is identical to the formulations that were used in the three clinical trials so there are no bioequivalence issues. Zentase formulation is composed of hypromellose delayed-release EC minitablets (or beads) in capsules or smaller beads in the case of pediatric strength capsule formulation.

Zentase is available in multiple dosage strengths (5,000, 10,000, 15,000 and 20,000 lipase units/capsule). The active ingredient in Zentase formulation is designed to be released at pH > 5.0 and delivered to the duodenum. The pediatric capsule (5,000 lipase units dose strength formulation) was tested for its content to be sprinkled on food for easier administration to young children.

IV. Clinical Efficacy: **(**The following information was obtained from Dr. Marjorie Dannis, the MO of GI division**)**.

The pivotal (EUR-1008-M; n=34) study showed that there was overall improvement in the clinical symptoms of EPI after treatment with Zentase as compared with placebo. The CFA for patients treated with Zentase was higher (88.28%) than for patients treated with placebo (62.76%), a mean difference in CFA (ΔCFA) of 25.5% increase.

For supportive study, EUR-1009-M, the primary efficacy endpoint was the percentage of "responders", defined as those patients without steatorrhea and without signs and symptoms of malabsorption after one and two weeks of treatment.

The results obtained from this supportive study showed that the percentage of responders on Zentase (57.9%; 11/19) was consistent with the percentage of responders under previous treatment (68.4%; 13/19). The results of the analysis of fecal fat content (a component of the definition of responder) after dose-stabilization and a second week of treatment with EUR-1008 were similar (27.0 ± 7.5% and 27.3 ± 6.6%, respectively) and were not statistically significantly different.

V. Clinical Safety: **(**The following information was obtained from Dr. Marjorie Dannis, the MO of GI division**)**.

The majority of the patients (27/34, 79.4%) experienced at least one adverse event (AE) while receiving Zentase compared with patients (16/32, 50.0%) experiencing at least one AE while receiving placebo. The safety data showed four most common AEs, 3 for GI disorders, i.e., abdominal pain, flatulence, abdominal distension, and one for Nervous system disorders, headache. In general, the safety profiles obtained from the pivotal clinical trial as well as from the supportive study EUR-1009-M were found acceptable.

2. Question Based Review

2.1 General Attributes

Background

EPI is a syndrome characterized by poor absorption of fats, proteins, and to a lesser extent, carbohydrates, which manifests primarily in patients with cystic fibrosis (CF) or with CP. EPI is caused by a progressive loss of pancreatic cells that produce digestive enzymes either from damage to pancreatic aciner cells, occlusion of the pancreatic ducts, trauma to the pancreas, or surgery of the gastrointestinal system in which portions of the stomach or pancreas are removed. Treatment of EPI patients using pancreatic enzyme products (PEPs), which are derived from pigs and contain mixtures of pancreatic lipase, amylase and protease, has been reported over the last three decades.

Several PEPs are currently on the US market without approval since these PEPs were developed before the Food and Drug Administration (FDA) approval requirements for NDAs were enacted in 1938. In 2004, FDA requested manufacturers of PEPs to submit an NDA for approval of these products.

Drug Substance:

The drug substance in Zentase formulation is porcine-derived pancreatic enzyme.

Formulations:

Zentase capsule contains beads which is enteric-coated with no overfill of product in each capsule and the beads are designed to dissolve at pH values above 5. Zentase is available in multiple dosage strengths (10,000, 15,000 and 20,000 lipase units) as well as a pediatric formulation (5,000 lipase units), which was developed and tested to be sprinkled on food for easier administration to young children.

Mechanism of Action:

Treatment of EPI patients uses pancreatic enzyme products (PEPs) as a replacement therapy. Zentase is designed to deliver pancreatic enzymes to the duodenum, where they help digest fats, proteins, and carbohydrates in food by breaking them down into smaller substances that can be absorbed from the small intestine.

Indication:

Zentase is indicated in patients with partial or complete exocrine pancreatic insufficiency associated with

- Cystic fibrosis
- Chronic pancreatitis due to alcohol abuse 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)
- Intestinal failure

Dosing Regimen:

The recommended starting dose of Zentase in patients age 7 and older is 1,000 lipase units/kg of body weight/meal, with a total dose less than or equal to 10,000 lipase units/kg of body weight/day. Patients may also determine their dose by monitoring consumption of fat and should not exceed 4,000 lipase units/g fat/day.

Zentase capsules must be swallowed intact with food (or sprinkled on food, if necessary) and with adequate amounts of liquid. Sponsor proposes that patients on other pancreatic enzyme

products may be switched to Zentase using doses that are comparable initially and it should be subsequently adjusted, as necessary, based on the control of symptoms.

2.2 General Clinical Pharmacology

***In Vivo* Intubation Study:**

Q1. What is the Bioavailability (Bioactivity) of Zentase MT Capsules obtained from *in vivo* Intubation Study PR001?

The bioavailability data of all 8 patients who completed the study and were considered evaluable "per protocol" (PP population) were analyzed. The difference in amount of lipase recovered between the treatments, (Zentase+Food) and (Food only), was obtained. Bioavailability (BA in %) of Zentase was calculated as the difference in the amount of lipase (i.e., exogenous) recovered in duodenum and expressed as the fraction of the administered Zentase dose.

The mean BA was calculated to be 21.6% with a large intersubject variation ranging from -51.9% to 71.4%. Additional analysis for these patients was also performed by the sponsor, and presented in the table below, i.e., patients with a mean "normal" duodenal pH range (>5.0; n=6) excluding patients with "low" mean duodenal pH (<4.0; n = 2). The mean BA for the 6 patient with a mean duodenal pH> 5.0 was found to be 33.7% with a smaller intersubject variation ranging from 10.8% to 71.4%.

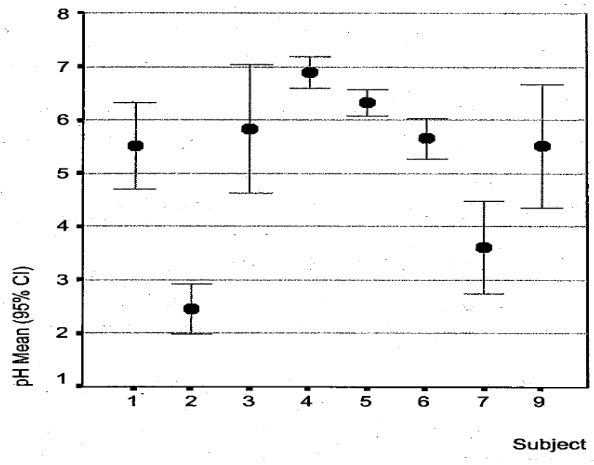
Table 4. Lipase Recovered by Treatment (PP, n=8 and Normal pH population, n=6)

Patient No.	**Lipase Recovered (units)**		**Bioavailability (%)**
	Zentase + Food	**Food only**	
001	27,480	20,041	10.82
002	0*	834	-1.22
003	99,900	50,853	71.4
004	20,318	336	29.1
005	52,292	684	63.1
006	25,534	4,551	30.5
007	0	35,718	-51.9
009	33,822	19,152	21.3
N=8 (Per protocol)	32,418 (± 32,229) (0-99,900)	16,521 (± 18,779) (336-50,853)	21.6 (±38.5)
N=6 (normal pH) (excluding patient #s 2 &7)	43,224 (± 29,894) (0-99,900)	15,936 (± 19,245) (336-50,853)	33.7 (±24.1)

*. Number in blue: after recalculation to subtract the amount recovered in gastric aspirate.

Patient Nos. 2 and 7 had lower mean duodenal pH values (<4.0) as shown below.

Figure 1. Mean (95% CI) pH Values of Patients with Ensure Plus and Zentase



Lower BA% found in these 2 patients could be due partly to a lower duodenal pH values since the Zentase is designed to release lipase at pH >5.0.

Reviewer's Comments:

1. The bioavailability study is not acceptable for the following reasons:

(A) The quantity of lipase recovered in one patient following administration of food only was ~35,000 units which was substantially greater than that (zero units) following administration of Zentase with food. Even if the lipase was not released due to the low duodenal pH in this subject, this does not explain "zero" lipase recovery when Zentase was given with the 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. 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.

***In Vitro* Stability Study**

Q2. Does *In vitro* Stability Testing of Zentase Content Sprinkled on Food Support the Statement Proposed in the Label, (b) (4)

The results of *In vitro* stability study showed acceptable stability data for Zentase content mixed and tested with several types of food (pH ≤ 5.0) for 60 min to support the proposed labeling.

The influence of the contact of different common types of baby foods with Zentase EC capsules (5,000 units USP/capsule) was studied. The pH testing for common types of foods was carried out and the results are shown below:

Table 5. Eleven Types of Food were Selected and Tested with Zentase Content

Food Type	Brand	Trader	Code/Batch	pH
Applesauce	Granny Smith flavored apple sauce	MOl's	0605WA	3.5-4.0
Applesauce	Applesauce 1st Foods	Gerber	US71316FK	3.5-4.0
Bananas	Bananas-1st Foods	Gerber	US71355FK	4.3-4.8
Pear	Pears- 1st Foods	Gerber	US71345FK	3.5-4.0
Pudding Vanilla/Apples	Vanilla Custard Pudding with Apples-Stage 2	Beech-Nut	B0237B0828	3.8-4.5
Vanilla Pudding	Vanilla Custard Pudding	Gerber	US450 2F2 0757	>5.5- 6.1
Banana Pudding	Banana Pudding Stage-3	Beeh-Nut	E0521C1123	4-4.5
Banana juice/yogurt	Mixed fruit Medley with yogurt	Gerber	US893 1F6 1750	3.9-4.5
Mixed fruit juice/yogurt	Mixed fruit juice/ yogurt	Gerber	US897 1F6 0122	3.1-4.5
Grated apple with sugar and lemon	-----	-----	-----	3.4-3.5
Smashed banana with sugar and lemon	-----	-----	-----	4.5-5.0

Ten out of 11 food types (except vanilla pudding) showed pH ≤5.0. Those 10 food types were then used for *in vitro* stability test. After Zentase content being mixed with foods for 60 min, the beads were rinsed with pH 1.2 buffer and tested for dissolution using USP method (Parts 1 and 2). The results of USP dissolution testing are shown below (Part 2 only):

Table 6. In Vitro Stability Study for Zentase Content when Mixed with Several Types of Food for 60 minutes

Batch Nos.	**USP Dissolution Part 2 (pH 6.0 for 30 min)**		
	P200550387	**P200550348**	**P200550668[1]**
Food Type	**Mean (CV) % dissolved[2]**		
Applesauce Mott's	100 (1.5)	94 (1.0)	92 (3.0)[2]
Applesauce Gerber	98 (1.5)	98 (1.5)	89 (1.2)
Bananas	99 (1.1)	99 (1.1)	89 (3.0)
Pear	99 (1.8)	99 (1.8)	98 (2.8);
Pudding Vanilla/Apples	102 (2.7)	102 (2.7)	91 (1.0)
Banana Pudding	102 (2.5)	102 (2.5)	91 (5.0)
Banana juice/yogurt	99 (0.6)	99 (0.6)	90 (1.4)
Mixed fruit juice/yogurt	96 (5.1)	96 (5.1)	94 (1.3)
Grated apple with sugar and lemon	92 (2.0)	92 (2.0)	88 (0.9)
Smashed banana with sugar and lemon	100 (2.2)	100 (2.2)	91 (5.3)
Range of the Means	92-102	92-102	88-94

[1]. Batch No. P200550668 was used for production of 5,000 units USP lot No. P200550785 used for Study PR-001 study and EUR-1009-M.

[2]. A mean of 6 readings per batch.

Reviewer's Comment:

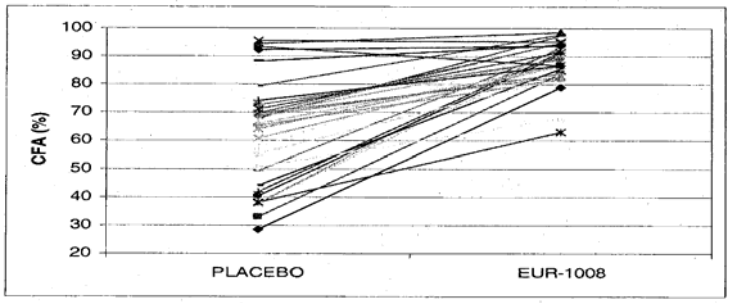
The data presented for *In vitro* stability study for Zentase content when mixed with food for 60 min was identical. The mean (CV%) values (and their raw data) of 9 out of 10 types of food tested for batch No. **P200550387** and **P200550348** (numbers in blue) were all identical (Table 6 above). Information request for clarification was made to the sponsor but the sponsor has not responded to this request.

Clinical Outcomes (The clinical efficacy and safety data was reviewed by Dr. Marjorie Dannis, the MO of GI division.**)**

Q 3: What were measured for Clinical Efficacy? What were the outcomes in the two clinical trials?

In the clinical trials, patients were titrated to effect. In Study EUR-1008-M, the primary efficacy endpoint was CFA, which was defined as [(fat intake - fat excretion)/fat intake] x 100% over the 72 hours. The CFA for patients treated with Zentase was higher (88.28%) than for patients treated with placebo (62.76%), a mean difference in CFA (ΔCFA) of 25.5% increase. Plots of the individual values of CFA under placebo and Zentase (EUR-1008) are shown below.

Figure 2. Plots of the Individual Values of CFA under placebo and Zentase (EUR-1008)



For the supportive Phase III study (EUR-1009-M) in very young children, the primary efficacy analysis focused on the percentage of responders, defined as those patients without steatorrhea (defined as <30% fecal fat content) and without signs and symptoms of malabsorption after one and two weeks of treatment compared with the previous treatment (Visit 3). The results of the analysis of fecal fat content (a component of the definition of responder) after dose-stabilization (Visit 3) and a second week of treatment with Zentase were very similar (27.0 ± 7.5% and 27.3 ± 6.6%, respectively) and were not statistically significantly different.

The results obtained from this supportive study showed that the percentage of responders on Zentase (57.9%; 11/19) was consistent with the percentage of responders under previous treatment at visit 3 (68.4% 13/19).

Q 4. What were the adverse events observed in the clinical trials?

The safety data from the two clinical trials were reviewed by Dr. Marjorie Dannis, the Medical Officer of the GI Division.

There are four most common AEs, three for GI disorders, i.e., abdominal pain, flatulence, and abdominal distension, and one for Nervous system disorders, i.e., headache. They are higher in Zentase treatment group than in placebo group. However, it should be noted that the mean patient exposure to Zentase was different, 29.7 days, compared with a mean exposure of 6.3 days on placebo. In general, the safety profiles obtained from the pivotal clinical trial as well as from the supportive study EUR-1009-M and *In Vivo* intubation study PR-001 were found acceptable by the Medical Officer.

2.3 Intrinsic Factors: Data not available

2.4 Extrinsic Factors: Data not available

2.5 General Biopharmaceutics:

The commercial Zentase product is identical to the formulations that were used in the clinical trials and is to be registered for the US market, however, this Zentase formulation (EUR-1008) has not been commercially available in any countries. Zentase capsule formulation (EUR-1008) is composed of hypromellose delayed-release EC minitablets (or beads) of pancrelipase USP and compendial excipients in a compressed form. For pediatric formulation of the 5000 lipase units dose strength, the same compositions, but small beads were used

The active ingredient in Zentase formulation (EUR-1008), pancrelipase USP, is designed to be released at pH > 5.0 and delivered to the duodenum. Zentase is available in multiple dosage strengths (5,000, 10,000, 15,000 and 20,000 lipase units/capsule) without overfill. The pediatric capsule formulation (5,000 lipase units) was tested for its content to be sprinkled on food for easier administration to young children.

2.6 Analytical Section

Q5. Is analytical method used acceptable?

The analytical method using (b) (4) as a substrate for lipase determination was validated and is found acceptable.

Linear kinetics of fatty acid release by the lipase and titration by NaOH as a function of time were observed and the lipase activity is estimated from the micromoles of

NaOH added per unit time (slope of the titration curve; 1 IU = 1 μmole per minute). The above assay method is available in the literature since 1993. This method is essentially the same as the one used in the standard USP lipase assay, except that the substrate (olive oil- (b) (4)) and the assay pH value (b) (4) are different.

The results of assay validation are summarized below:

- The intra-assay precision (%CV) (QC samples, 30, 15, 7.5, and LLOQ, 5 U/mL) was 7.30, 4.96, 10.25, & 12.24% respectively. The corresponding accuracy figures were 98.59, 105.03, 105.49, & 105.29%.
- The inter-assay precision was 9.24, 10.39, 9.50, & 10.65% respectively. The corresponding accuracy figures were 98.11, 102.21, 100.67 & 102.46% respective\y.
- Recovery data is obtained by using sample (baseline + 16.0 U/mL) is expressed in percentage recovery and figures are 113.33, 93.33, 86.67, 100.00, 86.67, and 100.00 respectively.
- The Lower Limit of Quantitation for Lipase was 5U/mL.
- The assay was linear over the range 40 to 0 U/mL.

Reviewer's Comment:

The assay method does not differentiate human pancrelipase from the exogenous pancrelipase.

3. Detailed Labeling Recommendations

The labeling proposed by the sponsor will be reviewed at a later time.

4. Appendices

4.1 Proposed Package Insert (Original and Annotated)

4.2 Individual Study Review

4.3 Cover Sheet and OCPB Filing/Review Form

NDA 22-210 for Zentase (Pancrelipase) MT Capsules

Appendix 4.1

Proposed Labeling

29 pp withheld in full immed. after this page as (b)(4) Draft Labeling.

NDA 22-210 for Zentase (Pancrelipase) MT Capsules

Appendix 4.2

Synopses of Individual Studies

In Vivo Intubation Study PR-001

Study of the Gastrointestinal Bioavailability of a Novel Pancreatic Extract Product (EUR-1008) in Chronic Pancreatitis Patients with Exocrine Pancreatic Insufficiency	
Investigational Product:	EUR-1008 (Zentase™)
Intended Indication Studied:	chronic pancreatitis
Study Design:	open-label, randomized, single center, single treatment, cross-over trial
Name of Sponsor:	Eurand S.p.A.
Protocol Number:	PR-001
Clinical Development Phase:	Phase 3
Study Initiation Date:	6 September 2007
Study Completion Date:	26 November 2007
Name and Affiliation of Principal Investigator:	Phillip Toskes, MD University of Florida Division of Gastroenterology, Hepatology & Nutrition
Date of Report:	06 December 2007

This study was performed in compliance with Good Clinical Practice (GCP) including the archiving of essential study documents. This Clinical Study Report follows guidelines outlined by the International Conference on Harmonization.

Synopsis

Name of Company:	Eurand S.p.A.
Name of Finished Medicinal Product:	EUR-1008 (Zentase ™)

Name of Active Ingredient(s):	Pancrelipase
Title of Study:	Study of the Gastrointestinal Bioavailability of a Novel Pancreatic Extract Product (EUR-1008) in Chronic Pancreatitis Patients with Exocrine Pancreatic Insufficiency
Investigator:	Phillip Toskes, MD
Study Center(s):	Shands Hospital, University of Florida
Publication (reference)	None
Studied Period (years):	September 6, 2007 November 26, 2007
Phase of development:	1
Objectives:	Efficacy Objectives: The main objective of the study was to determine the gastrointestinal bioavailability of EUR-1008 (Zentase™) in fed conditions in chronic pancreatitis patients with exocrine pancreatic insufficiency. The study also determined if cholecystokinin (CCK) blood levels were affected following the administration of EUR-1008. Safety Objectives: The safety objectives were to compare the frequency, duration, and severity of treatment-emergent adverse events and the changes in clinical laboratory findings.
Methodology:	This study was an open-label, randomized, single center, single treatment, 2x2 cross-over trial. The study sample consisted of male or female adult chronic pancreatitis patients with EPI. The study consisted of a screening period and of a 5-6 day hospitalization period, with two separate gastroduodenal perfusion procedures. Day 1: Patients after signing an informed consent, entered the General Clinical Research Center (GCRC) at the Shands Hospital, University of

	Florida. The Principal Investigator (PI) evaluated the eligibility of the patient for the trial, and medical history, physical examination, and blood and urine samples were collected. Exclusionary drugs (PPIs, antacids and drugs capable of altering GI motility) were discontinued 7 days prior to entering the GCRC. Day 2: Patients were randomized to receive either Ensure Plus™ alone or Ensure Plus™ with EUR-1008 according to a predetermined randomization scheme. The dose of EUR-1008 was 75,000 USP lipase units (three capsules containing 20,000 units each plus three capsules containing 5,000 units each) per procedure. The capsules were opened and their contents mixed with 480 ml of Ensure Plus™ immediately before administration. Day 3: Washout day. An abbreviated physical exam was done on this day. Day 4: The same procedures of day 2 were repeated. Patients that received Ensure Plus™ alone on day 2, received Ensure Plus™ with EUR-1008 on day 4 or vice-versa. Day 5: Complete physical exam and blood and urine samples were collected. Patients were discharged. The bioavailability of EUR-1008 was estimated by comparing the recovery of lipase, amylase and chymotrypsin in the two treatment groups (Ensure Plus™ alone and Ensure Plus™ with EUR-1008) after administration of the test meal.
Number of Subjects (planned and analyzed):	12 evaluable male or female adult patients were planned, and 11 patients were enrolled, 10 of whom were treated and had post-treatment data collected. Two patients were excluded from the efficacy analysis (one outlier and one because of a violation in the I/E criteria). The "per protocol" population therefore included 8 patients. The data from all patients were analyzed in safety analyses.
Diagnosis and main criteria for inclusion:	Patients of either sex over the age of 18 with a history compatible with chronic pancreatitis with exocrine pancreatic insufficiency and significant steatorrhea or fecal elastase below 100 mcg/g.

Test product, dose and mode of administration, batch number:	EUR-1008 was administered orally with 480 ml of Ensure Plus as a single fixed dose of 75,000 USP lipase units per procedure per patient (the content of three capsules of 5,000 USP lipase units plus the content of three capsules of 20,000 USP lipase units). Batch Number: [20,000 USP units: 058761C; 5,000 USP units: 058755B]
Duration of treatment:	One administration
Comparison procedure, dose and mode of administration, batch number:	480 ml Ensure Plus™ alone, orally
Criteria for evaluation: **Efficacy:** **Safety:**	 Primary efficacy endpoint (bioavailability of EUR-1008) was estimated from the amount of lipase released and recovered in the duodenum following administration of EUR-1008 in fed conditions (lipase output). Secondary efficacy endpoints were also determined following administration of EUR-1008 in fed conditions. These included the evaluation of the amount of amylase and chymotrypsin released and recovered in the duodenum (amylase output and chymotrypsin output), the measurement of cholecystokinin (CCK) levels in blood, and the measurement of gastric and duodenal pH. Safety was evaluated in terms of the occurrence of adverse events (AEs) and changes in clinical laboratory parameters, physical examination findings, and vital sign measurements.
Statistical methods:	Descriptive statistics of the various parameters and the corresponding lower and upper 95% confidence intervals (CI) were computed. For continuous variables, descriptive statistics included for each treatment sequence included: mean, standard deviation, median, lower and upper 95% CI, minimum, maximum, number of non-missing observations. The descriptive statistics for dichotomous or categorical variables were

	numbers and percentages of each of the scores or categories for each treatment. The bioavailability of EUR-1008 was estimated by comparing the recovery of lipase, amylase and chymotrypsin in the two treatment groups (Ensure Plus™ alone and Ensure Plus™ with EUR-1008) after administration of the test meal. Statistical significance was evaluated by means of a paired samples t-test. All AEs were listed, and the frequency of treatment-emergent AEs was tabulated by system organ class and preferred term. All laboratory data were listed and analyzed using the appropriate statistical methods.
–SPONOSR'S CONCLUSIONS **Efficacy Results:** **Safety Results:**	The mean bioavailability in the "per protocol" population for lipase, amylase and chymotrypsin was 27.5%, 21.6% and 40.1 respectively. In the "Normal GI pH" subpopulation (i.e. patients with mean duodenal pH greater than 4) mean bioavailability of lipase was 45.6%. The difference between treatment groups was statistically significant for all enzymes in the "Normal pH" group and for amylase and chymotrypsin also in the "per protocol" population. No difference in the CCK values between the two treatments was observed. EUR-1008 was generally well tolerated by the study patients at the dose tested. All of the adverse events reported by study patients were mild and transitory. No trends were evident in adverse events, vital signs, or clinical laboratory tests. No clinically important changes in clinical laboratory tests, vital signs, or body weights were observed with the EUR-1008 dose.

Reviewer's Comments: We do not agree with the sponsor's conclusion on the bioavailability findings.

NDA 22-210 for Zentase (Pancrelipase) MT Capsules

Appendix 4.3

Cover Sheet and OCP Filing Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-210**	**Brand Name**	**Zentase**
OCPB Division (I, II, III)	**DCP III**	**Generic Name**	**Pancrelipase**
Medical Division	**GI**	**Drug Class**	**Pancrelipase Enzyme Products**
OCPB Reviewer	**Tien-Mien Chen, Ph.D.**	**Indication(s)**	**Exocrine Pancrelipase Insufficiency**
OCPB Team Leader	**Sue-Chih Lee, Ph.D.**	**Dosage Form**	**Capsules**
		Dosing Regimen	**Pancreatic enzyme replacement therapy**
Date of Submission	**12/14/07**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**06/09/08**	**Sponsor**	**Eurand**
Medical Division Due Date	**06/10/08**	**Priority Classification**	**P**
PDUFA Due Date	**06/17/08**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	1	1	
I. Clinical Pharmacology				
Mass balance:				

Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
HEALTHY VOLUNTEERS-				
single dose:				
multiple dose:				
Patients-	**X**			
single dose:		**1**	**1**	
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				

Relative bioavailability -	X			
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**	**1**	***In vitro* stability study**
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**	**3**	**Including analytical report.**

Filability and QBR comments

	"X" if yes	***Comments***
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. IRs

QBR questions (key issues to be considered)	1. What is the bioavailability (bioactivity) of Zentase MT capsules obtained from duodenum in vivo ? 2. Does *In vitro* Stability Testing of Zentase content sprinkled on food support the statement proposed in the label?
Other comments or information not included above	
Primary reviewer Signature and Date	**Tien-Mien Chen, Ph.D. 06/11/08**
Secondary reviewer Signature and Date	**Sue-Chih Lee, Ph.D. 06/11/08**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tien-Mien Chen
6/11/2008 08:28:32 PM
BIOPHARMACEUTICS

Sue Chih Lee
6/11/2008 08:32:28 PM
BIOPHARMACEUTICS