U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-210 / 000
Drug Name:	Zentase Pancreatic Enzyme Product Delayed-Release Capsules (EUR-1008)
Indication(s):	Exocrine Pancreatic Insufficiency (EPI)
Applicant:	Eurand Pharmaceuticals Limited (EPL)
Date(s):	Letter Date: 12/14/2007
	Stamp Date: 12/17/2007
	Date Forwarded to DDR: 12/19/2007
	Date Received by Reviewer: 4/21/2008
	PDUFA Date: 6/17/2008
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Freda W. Cooner, Ph.D.
Concurring Reviewers:	Mike Welch, Ph.D.
Medical Division:	Division of Gastroenterology Products
Clinical Team:	Marjorie F. Dannis, M.D., Medical Reviewer
	Anne Pariser, M.D., Team Leader
Project Manager:	Maureen Dewey

Keywords: Clinical studies, NDA review, Crossover design, Repeated measure ANOVA, Subgroup analyses

Table of Contents

1. EXECUTIVE SUMMARY 3

1.1 CONCLUSIONS AND RECOMMENDATIONS 3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES 3
1.3 STATISTICAL ISSUES AND FINDINGS 4

2. INTRODUCTION 4

2.1 OVERVIEW 4
2.2 DATA SOURCES 6

3. STATISTICAL EVALUATION 6

3.1 EVALUATION OF EFFICACY 6
3.1.1 Study Design and Endpoints 6
3.1.2 Patient Disposition, Demographic and Baseline Characteristics 8
3.1.3 Statistical Methodologies 9
3.1.4 Results and Conclusions 11
3.2 EVALUATION OF SAFETY 11

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS 11

5. SUMMARY AND CONCLUSIONS 13

APPENDIX 14

1. EXECUTIVE SUMMARY

The sponsor has submitted a pivotal study EUR-1008-M in patients aged 7 years or higher at the time of enrollment and a supportive study EUR-1009-M in pediatric patients to evaluate the safety and efficacy of the Eurand pancreatic enzyme product (PEP). This review will mainly discuss the pivotal study.

1.1 Conclusions and Recommendations

The pivotal study showed that EUR-1008 was effective in increasing coefficient of fat absorption (CFA) level compared to Placebo. However, for patients with the primary efficacy endpoint of CFA greater than 80 following oral administration of Placebo, the effect of treatment EUR-1008 was minimal and so it is not clear that EUR-1008 would be beneficial to patients presenting with high levels of CFA.

1.2 Brief Overview of Clinical Studies

The pivotal study EUR-1008-M was a randomized, double-blind, placebo-controlled, two-treatment, crossover, multicenter study to evaluate the safety and efficacy of Eurand pancreatic enzyme product (PEP) in cystic fibrosis (CF) patients with exocrine pancreatic insufficiency (EPI). Patients were treated for a total of approximately 30 days of which 7 were in randomized, double-blind treatment at a dose determined by titration to achieve control of symptoms of malabsorption. The study enrolled 34 patients in total in 12 US study centers; a total of 33 patients were randomized; 32 patients completed both treatment periods and are included in the efficacy analysis population. One patient received treatment EUR-1008 (first treatment) but then voluntarily withdrew consent. All patients enrolled are between 8 to 23 years of age at the time of enrollment and 32 of them are white; 17 of which are male and 17 are female. This statistical review is focused on this study.

The supportive study EUR-1009-M was an open-label, non-randomized, multiple-dose, single-treatment, multicenter study in pediatric patients younger than 7 years with CF and EPI. Patients were treated for a total of approximately 14 days at a dose determined by titration to achieve control of symptoms of malabsorption. Ten US study centers enrolled 19 white patients with ages from one to six to compare measures of malabsorption of fat in CF patients with EPI after administration of EUR-1008 versus a baseline therapy (with currently available PEPs). Out of the 19 patients, 12 are male and 7 are female. All 19 patients completed the study. The number of responders (patients with less than 30% fecal fat content and without signs and symptoms of malabsorption) at baseline (under currently available PEPs) was 10/19 (52.6%), 13/19 (68.4%) after one week of treatment (stabilization) and 11/19 (57.9%) after the second week of treatment with EUR-1008. The mean fecal fat content was 24.8% at baseline, 27.0% after stabilization, and 27.3% after the second week of treatment. The efficacy of EUR-1008 in this patient population seems consistent with that of currently available PEPs. No safety signal was raised from the study. There is no statistical concern regarding this study. Results should be considered descriptive only. For more details on this study, please refer to the separate clinical review.

A preclinical study PR-001 was also completed. It was a randomized, open-label, single treatment, crossover study to determine the gastrointestinal bioavailability of EUR-1008 in chronic pancreatitis (CP) patients with EPI. The study enrolled 11 patients in one US center. For more details on this study, please refer to the separate clinical and pharm/tox reviews.

1.3 Statistical Issues and Findings

The pivotal study EUR-1008-M was a crossover study and so each patient would receive both treatments (EUR-1008 and Placebo). The sponsor has treated these two sets of outcomes from two treatments as independent for the treatment effect comparisons while for such a crossover design the correlation between the outcomes from two treatments are not ignorable. However, t-test of the outcome differences paired up by each patient was performed and the conclusion was not altered. Results from both approaches have been presented in this statistical review.

It was observed that the treatment effect has a linear relationship with the baseline condition. In particular, for the primary endpoint of CFA the change (increase) after treatment EUR-1008 compared with that after Placebo is decreasing with the CFA after Placebo. Especially for patients with CFA > 80 following oral administration of Placebo, the effect of treatment EUR-1008 was minimal. Five patients who finished the study were in this category and two of which had a decrease in CFA as opposed to an expected increase. A categorical analysis has been performed and presented in this statistical review.

Additional analyses including subgroup studies by sequence and period are also performed and presented in this statistical review. No impact from these two factors was observed.

2. INTRODUCTION

2.1 Overview

Exocrine pancreatic insufficiency (EPI) is a syndrome characterized by poor absorption of fats, protein, and to a lesser extent, carbohydrates, which manifests primarily in patients with cystic fibrosis (CF) or chronic pancreatitis (CP). CF was therefore considered a model of EPI for the clinical development of EUR-1008. While the prominent features of CF are due to the affected cells of the respiratory tract, a majority (approximately 85%) of patients also exhibit signs of EPI. EPI is characterized by severely decreased secretion of pancreatic digestive enzymes due to impaired fluid secretion and obstruction of pancreatic ducts by dehydrated aggregates of secreted proenzymes. The most common mutation observed in CF, delF508, is highly associated with pancreatic insufficiency.

Treatment of EPI in patients with CF using pancreatic enzyme products (PEPs) has been will established over the last three decades. PEPs are typically derived from pigs and contain mixtures of pancreatic lipase, amylase, protease, and other enzymes. The sponsor has stated that numerous nonrandomized and randomized open-label or blinded studies have shown that enteric-

coated microspheres (b) (4)

Only three randomized, double-blind, placebo-controlled studies of PEPs for treatment of EPI in CF patients have been reported. Taken together, the sponsor has claimed that the results in those studies provide clear evidence of the efficacy of different PEP products for the treatment of EPI. The drugs appeared to have good, short-term safety profiles, with the exception of a potentially clinically relevant proportion of cases of hyperuricosuria.

Although the short-term safety of PEPs appears good, the long-term use of high doses of PEPs has been associated with increased risk of developing fibrosing colonopathy. The 1995 joint recommendations of the FDA and the Cystic Fibrosis Foundation (CFF) specified a starting dose of 1,500-2,500 lipase units/kg/meal, not to exceed 6,000 lipase units/kg/meal.

Because most PEPs were developed before current United States FDA approval requirements were enacted, and because of the possible safety risk of high-dose therapy, the FDA has determined that no PEP without an approved NDA will be allowed in the USA after April 2008. The FDA has also issued a Guidance in April 2006 regarding the content of the NDAs of PEPs, in which information about the required clinical trials is provided.

EUR-1008 is a novel, gastroprotected PEP with zero overfill, which has been developed to comply with the FDA Guidance for PEPs. EUR-1008 is intended for use in patients with partial or complete EPI. CF was chosen as a model condition of EPI to perform the Phase III clinical trials with EUR-1008, because of the characteristics of this patient population.

The pivotal study EUR-1008-M was designed to assess the efficacy and safety of EUR-1008 in CF patients with EPI aged 7 and older, with the intention to be submitted in conjunction with existing safety data as part of a 505(b) (2) NDA. A detailed protocol outline was submitted to FDA and discussed on October 28, 2004 prior to submission of the Investigational New Drug Application. Data on the efficacy and safety of EUR-1008 in CF patients with EPI younger than 7 years old were collected in a supportive trial (EUR-1009-M). In the present trial both a Minitabs and a Microtabs formulation of EUR-1008 were used. The Microtabs formulation was specifically designed for children to allow sprinkling of the drug on food, where necessary.

The focus of this statistical review is on the pivotal study EUR-1008-M, which is a randomized, double-blind, placebo-controlled, two-treatment, crossover, multicenter study. Patients were treated for a total of approximately 30 days of which 7 were in randomized, double-blind treatment at a dose determined by titration to achieve control of symptoms of malabsorption. The study enrolled 34 patients in total in 12 US study centers. Patient 117802 received EUR-1008 during the open-label dose titration/stabilization period, but then voluntarily withdrew consent before randomized treatment. A total of 33 patients were randomized. Patient 117801 received treatment EUR-1008 (first randomization treatment) but then voluntarily withdrew consent and so 32 patients completed both treatment periods and are included in the efficacy analysis population. Patient 108802 was withdrawn by the sponsor after the crossover treatment period and so a total of 31 patients completed the study.

2.2 Data Sources

Materials reviewed include study reports (EUR-1008-M and EUR-1009-M), Protocol EUR-1008-M, SAP EUR-1008-M, and additional statistical report of EUR-1008-M. Some additional information, including the labeling, and the data sets and SAS programs for both EUR-1008-M and EUR-1009-M, was submitted and is located at the Electronic Document Room at \\Fdswa150\nonectd\N22210\N_000.

3. STATISTICAL EVALUATION

The pivotal study EUR-1008-M lasted about 11.5 months. In particular, the first patient visit was on May 15, 2006 and the last patient visit November 28, 2006. The primary efficacy objective of this study was to compare the CFA following oral administration of EUR-1008 and Placebo in CF patients with EPI.

The secondary efficacy objectives of this study were to compare changes in the CNA, total cholesterol, calculated low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), fat-soluble vitamins, weight gain/loss and body mass index (BMI), and symptoms of EPI after the oral administration of EUR-1008 and Placebo. Quality of life (QoL) at the beginning and at the end of the trial was also evaluated.

The safety objectives were to assess the frequency, duration, and severity of treatment-emergent AEs, changes in clinical laboratory parameters, physical examination findings, and vital signs measurements in the safety population.

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

The pivotal study EUR-1008-M was a randomized, double-blind, placebo-controlled, two-treatment, crossover, multicenter study in CF patients with EPI. The study planned for a minimum of 30 male or female patients greater than or equal to 7 years of age, with a body weight less than or equal to 70 kg; a BMI greater than or equal to 20 kg/m^2 for ages 18 years and above or a BMI above the 25^{th} percentile for patients aged 7 through 17 years; and a confirmed diagnosis of CF and EPI.

The study included the following:

- Screening period (1 to 14 days)
- Washout period (2 days)
- Open-label dose titration/stabilization period (6 to 9 days)
- Randomization treatment period (6 to 7 days)
- Open-label normalization period 1 (5 to 14 days)
- Crossover treatment period (6 to 7 days)

- Open-label normalization period 2 (7 days)

The order of treatments (Placebo → EUR-1008 or EUR-1008 → Placebo) was determined by randomization at the beginning of the randomization treatment period only, and was continued through the crossover treatment period. During the study, all patients were instructed to consume a recommended diet that derived 45% of calories from fat, 20% of calories from protein, and 35% of calories from carbohydrates. During home treatment periods, patients or parents/legal guardians recorded daily food intake in a diary for review by the investigator. During the inpatient portions (stool collection period – starting on the morning of Day 3 for a 3- to 5-day hospital stay) of the randomization and crossover treatment periods, all food was prepared under the supervision of a nutritionist experienced in the treatment of CF patients. The type and amount of food consumed was closely monitored during this time.

The test product was EUR-1008 capsules for oral administration containing EUR-1008 Microtabs in a strength of 5,000 USP lipase units/capsule or EUR-1008 Minitabs in strengths of 10,000, 15,000 or 20,000 USP lipase units/capsule. The starting dose was approximately 1,000 lipase units/kg/meal, with a total dose less than or equal to 10,000 lipase units/kg/day (not to exceed 4,000 lipase units/g fat/day). Patients were administered combinations of capsules with different dosing strengths, as required to achieve control of their signs and symptoms of EPI.

Patients were treated with EUR-1008 during the open label dose titration/stabilization period, the open label normalization periods 1 and 2, and during the randomized treatment period or the crossover period (according to the randomized treatment sequence). The mean exposure to EUR-1008 was 29.7 days and to Placebo was 6.3 days.

The primary efficacy endpoint was the comparison of the CFA after administration of EUR-1008 versus Placebo. The CFA was determined on Days 3, 4, and 5 of the randomization treatment period and the crossover treatment period, and was based on the intake of fat calculated from the dietary record and excretion of fat determined from 72-hour stool samples.

After the administration of EUR-1008 and Placebo, secondary assessments included the comparison of and change in a) the CNA, b) blood levels of total cholesterol, calculated LDL-C, HDL-C, fat soluble vitamins (A, E) and PIVKA II, c) weight gain/loss and BMI, and d) the incidence of clinical symptoms of EPI (stool frequency and consistency; intestinal bloating, pain, and flatulence). QoL was also evaluated at the beginning and at the end of the trial.

The efficacy analysis population consisted of all randomly assigned patients who received treatment and completed at least one post-baseline measurement for each period of the treatment sequence. Patients were to be analyzed according to the randomized treatment sequence. However, all patients received treatment as planned. The efficacy analysis population included 32 patients and was used in the analysis of the following efficacy endpoints: CFA, CNA, and clinical symptoms of EPI. The safety analysis population consisted of all patients who received at least one dose of study drug. All safety analyses were based on the safety population, which included 34 patients.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Twelve US study centers enrolled 34 patients (safety population) in this study. Patient 117802 received EUR-1008 during the open-label dose titration/stabilization period, but then voluntarily withdrew consent before randomized treatment. A total of 33 patients were randomly assigned to one of the two sequences (Placebo → EUR-1008 or EUR-1008 → Placebo). Patient 117801 received EUR-1008 through the randomization treatment period and then voluntarily withdrew consent during open-label normalization period 1. Thirty-two (32) patients (94.1%) completed both the randomization and the crossover treatment periods and are included in the efficacy analysis population. Patient 108802 was withdrawn by the sponsor after the crossover treatment period when it was determined that the patient had a surgical history of sigmoid colectomy and did not meet exclusion criterion #8. A total of 31 patients (91.2%) completed the study.

The protocol states that patients who withdrew prior to study completion were to be replaced to obtain a minimum of 30 eligible and evaluable patients. The minimum number of patients was maintained after the withdrawal of these three patients, so no additional patients were enrolled.

A total of 135 protocol deviations and 30 violations occurred during this study. The sponsor has claimed that these did not impact the assessments of safety and efficacy in this study and there was no potential concern for patient safety.

The most common deviation was study visits that occurred outside the visit window (63 deviations of 135). Nineteen (19) of these deviations were related to the response time of the lab that performed the fecal elastase measurements, and four of these deviations were related to time periods greater than the 14 days range. The sponsor has therefore concluded that the total number of 'true' deviations regarding study visits occurred outside the visit window was 48. The minimum and maximum for number of days out of the window was -4 days and +34 days.

The sponsor had claimed that overall, there was no potential concern for patient safety from the deviation. All patients who had a deviation completed the study and were included in the efficacy analysis population, with the exception of Patients 117801 and 117802 who both voluntarily withdrew before the end of treatment.

The most common protocol violation (16 violations of 30) was missing laboratory assessments. It was discovered shortly after the start of the study that the laboratory tests for phosphorous and serum uric acid were not part of several local laboratories' standard chemistry panels. The discrepancy was identified and resolved. All of the patients with protocol violations were included in the efficacy analysis population. The sponsor claimed that there were no notable safety findings.

Half of the patients in the safety and efficacy population were male and most of the patients [32/34 (94.1%) and 30/32 (93.8%), respectively] were white. Taking into account the safety population, the overall mean age for patients was 15.5 years with a minimum age of 8 years and a maximum age of 23 years. The breakdown of age categories included 7 patients (20.6%) who were 7 to 11 years of age, no patients who were 12 to 13 years of age, 13 patients (38.2%) who were 14 to 17 years of age, and 14 patients (41.2%) who were older than 17 years of age.

Patients had a mean height of 155.73 cm, a mean weight of 51.15 kg, and a mean BMI of 20.47 kg/m^2. The mean duration of CF was 14.0 years, with a range from 3 years to 23 years.

For pre-study medication, 20 of the 34 patients enrolled (58.8%) and 18/32 (56.2%) of the patients evaluable for efficacy were taking proton-pump inhibitors, anti-H2, or antacids, which are frequently used to improve the effect of pancreatic supplements. The most commonly reported concomitant medications during the EUR-1008 treatment periods were multivitamins, dornase alfa, salbutamol, and tobramycin. The most commonly reported concomitant medications during the Placebo treatment periods were the same with similar number of patients.

Treatment compliance was similar for both double-blind treatment periods and during treatment with EUR-1008 and during treatment with Placebo. The mean study drug compliance during treatment with EUR-1008 was 94.6% of the prescribed dose and during treatment with Placebo was 100.9% for both double-blind treatment periods.

3.1.3 Statistical Methodologies

The CFA observed during treatment with EUR-1008 and CFA observed during treatment with Placebo were compared using an ANOVA model for repeated measures with the treatment and sequence as fixed effects, and patient nested in a sequence as a random effect. CFA is defined as [(fat intake minus fat excretion) divided by fat intake] multiplied by 100. The least squares (LS) means and the estimates of the treatment contrasts (versus Placebo), associated *P* value, and 95% CI were presented.

Table 3.1 presents a summary of the CFA data by the aforementioned sponsor's model. The CFA (LS means) for patients treated with EUR-1008 (88.28%) was statistically significantly higher than for patients treated with Placebo (62.76%) ($P<0.001$). The difference in the CFA (LS means) of patients who received EUR-1008 and Placebo was 25.52 (95% CI: 19.32%, 31.73%). These results have been confirmed by this statistical reviewer.

Table 3.1 ANOVA Model Results of Coefficient of Fat Absorption (CFA, %)

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

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

Due to the fact that the ANOVA model shows no significant impact of 'sequence' on the results, instead of the model proposed by the sponsor a simple t-test for two independent samples may be

sufficient. Moreover, for such a crossover design, a paired t-test by each subject is considered more conventional. In this case, Patient 108802 is excluded from this population because it's lacking of Study Visit 8 (Placebo) outcome. Table 3.2 lists the results from the t-tests. It appears that two t-tests are consistent with the results from the ANOVA model and the significance difference between two treatment effects can still be concluded.

Table 3.2 T-test Results of Coefficient of Fat Absorption (CFA, %)

	Two independent sample t-test (EUR-1008 N=32, Placebo N=31)	**Paired t-test (N=31)**
Mean difference between EUR-1008 and Placebo	-25.58	-25.37
95% CI	(-32.91, -18.26)	(-31.63, -19.11)
P value	<0.001	<0.001

Source: Reviewer's Table

It is also interesting to know whether or not the 'sequence' and 'treatment period' have any impact on the outcomes and so the t-test results within sequences and treatment periods are summarized below in Table 3.3. The results show no visible impact of these two factors.

Table 3.3 T-test Results within Sequences and Periods of Coefficient of Fat Absorption (CFA, %)

	EUR-1008 (Period 1) (N=15)	**Placebo (Period 2) (N=14)**
Sequence 1 EUR-1008 → Placebo		
Mean (SEM)	86.98 (1.833)	63.13 (5.909)
SD	7.099	22.110
Median	86.75	66.35
Min, Max	67.8, 95.1	28.7, 95.5
	Two independent sample t-test within sequence 1 (EUR-1008 N=15, Placebo N=14)	**Paired t-test within sequence 1 (N=14)**
Mean difference between EUR-1008 and Placebo	-23.85	-23.28
95% CI	(-36.18, -11.52)	(-34.51, -12.05)
P value	<0.001	<0.001
	Placebo (Period 1) (N=17)	**EUR-1008 (Period 2) (N=17)**
Sequence 2 Placebo → EUR-1008		
Mean	62.39 (4.110)	89.48 (2.091)
SD	16.944	8.620
Median	65.79	91.49
Min, Max	37.9, 94.5	62.9, 98.7
	Two independent sample t-test within sequence 2 (EUR-1008 N=17, Placebo N=17)	**Paired t-test within sequence 2 (N=17)**

Table 3.3 T-test Results within Sequences and Periods of Coefficient of Fat Absorption (CFA, %)		
Mean difference between EUR-1008 and Placebo	-27.09	-27.09
95% CI	(-36.49, -17.70)	(-34.92, -19.27)
P value	<0.001	<0.001

	Two independent sample t-test within period 1 (EUR-1008 N=15, Placebo N=17)	**Two independent sample t-test within period 2 (EUR-1008 N=17, Placebo N=14)**
Mean difference between EUR-1008 and Placebo	-24.59	-26.35
95% CI	(-34.20, -14.97)	(-38.26, -14.45)
P value	<0.001	<0.001

Source: Reviewer's Table

3.1.4 Results and Conclusions

There was a significant overall improvement in the primary endpoint of CFA. For the major secondary efficacy endpoint of CNA, similar conclusion can be drawn as well (the results are presented in the Appendix).

3.2 Evaluation of Safety

Drug safety was assessed primarily by examining AEs, clinical laboratory parameters, physical examinations, and vital signs measurements. All safety analyses were conducted by the sponsor using the safety population. Data from the early termination visit was reported at the next scheduled visit at which the assessment was scheduled to occur. Patients were analyzed according to the treatment received at the time of event or evaluation. There is no statistical concern on the safety evaluation of the study EUR-1008-M.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

There is an obvious linear relationship between the treatment effect on CFA improvement and the CFA following administration of Placebo; in particular, the higher the CFA after administration of Placebo, the smaller improvement can be observed. The subgroup study in this section separates the efficacy population into three subpopulations based on the CFA following oral administration of Placebo ($CFA < 40$, $40 \leq CFA \leq 80$, $CFA > 80$). The results from both the ANOVA model proposed by the sponsor and the t-tests are listed in the following tables. Note that Patient 108802 did not have outcomes from Placebo treatment period and hence is excluded for this subgroup analysis. It appears that there is no significant improvement of CFA for the patients with $CFA > 80$ under Placebo, although the sample size is too small to make any definitive conclusion.

Table 4.1 ANOVA Model Results of Coefficient of Fat Absorption (CFA, %) Stratified by Placebo CFA

	EUR-1008	Placebo
Placebo CFA < 40	**(N=5)**	**(N=5)**
Mean (SEM)	81.88 (5.360)	35.07 (1.884)
SD	11.986	4.212
Median	83.73	37.73
Min, Max	62.9, 93.2	28.7, 38.3
LS means (SEM)	81.81 (4.395)	35.00 (4.395)
Difference between EUR-1008 and Placebo		-46.81
95% CI		(-62.38 -31.23)
P value		0.001
Placebo CFA in [40, 80]	**(N=21)**	**(N=21)**
Mean (SEM)	88.26 (1.464)	62.15 (2.441)
SD	6.707	11.184
Median	88.77	65.79
Min, Max	67.8, 97.8	40.5, 79.1
LS means (SEM)	88.04 (2.070)	61.93 (2.070)
Difference between EUR-1008 and Placebo		-26.11
95% CI		(-31.39 -20.83)
P value		<0.001
Placebo CFA > 80	**(N=5)**	**(N=5)**
Mean (SEM)	93.62 (1.988)	92.79 (1.260)
SD	4.445	2.817
Median	93.96	93.24
Min, Max	86.5, 98.7	88.2, 95.5
LS means (SEM)	93.73 (1.812)	92.90 (1.812)
Difference between EUR-1008 and Placebo		-0.83
95% CI		(-6.86, 5.20)
P value		0.722

Source: Reviewer's Table

Table 4.2 T-test Results of Coefficient of Fat Absorption (CFA, %) Stratified by Placebo CFA

	Two independent sample t-test	Paired t-test
Placebo CFA < 40	**(EUR-1008 N=5, Placebo N=5)**	**(N=5)**
Mean difference between EUR-1008 and Placebo	-46.81	-46.81
95% CI	(-59.91, -33.71)	(-62.38, -31.23)
P value	<0.001	0.001
Placebo CFA in [40, 80]	**(EUR-1008 N=21, Placebo N=21)**	**(N=21)**
Mean difference between EUR-1008 and Placebo	-26.11	-26.11

Table 4.2 T-test Results of Coefficient of Fat Absorption (CFA, %) Stratified by Placebo CFA

	Two independent sample t-test	**Paired t-test**
95% CI	(-31.86, -20.36)	(-31.39, -20.83)
P value	<0.001	<0.001
Placebo CFA > 80	**(EUR-1008 N=5, Placebo N=5)**	**(N=5)**
Mean difference between EUR-1008 and Placebo	-0.83	-0.83
95% CI	(-6.26, 4.60)	(-6.86, 5.20)
P value	0.733	0.722

Source: Reviewer's Table

The homogeneity among the study sites has been investigated by this statistical reviewer. The largest site had six patients while the smallest had only one. There is no visible impact from site on the outcomes, which very likely is due to the small sample size.

5. SUMMARY AND CONCLUSIONS

From the pivotal study EUR-1008-M, it can be concluded that there is an overall treatment effect on the primary efficacy endpoint of CFA and major secondary efficacy endpoint of CNA. However, whether or not EUR-1008 would improve CFA for the patients with CFA levels greater than 80 following oral administration of Placebo or under no treatment is questionable. Both the pivotal study EUR-1008-M and the supportive study EUR-1009-M have not raised any safety concerns.

APPENDIX

Table A.1 ANOVA Model Results of Coefficient of Nitrogen Absorption (CNA, %)

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

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

Table A.2 T-test Results of Coefficient of Nitrogen Absorption (CNA, %)

	Two independent sample t-test (EUR-1008 N=32, Placebo N=31)	Paired t-test (N=31)
Mean difference between EUR-1008 and Placebo	-21.53	-21.31
95% CI	(-27.71, -15.36)	(-26.71, -15.91)
P value	<0.001	<0.001

Source: Reviewer's Table

Table A.3 T-test Results within Sequences and Periods of Coefficient of Nitrogen Absorption (CNA, %)

	EUR-1008 (Period 1) (N=15)	Placebo (Period 2) (N=14)
Sequence 1 EUR-1008 → Placebo		
Mean (SEM)	85.82 (1.647)	64.49 (5.183)
SD	6.379	19.395
Median	87.72	70.03
Min, Max	68.6, 94.3	35.9, 89.9

	Two independent sample t-test within sequence 1 (EUR-1008 N=15, Placebo N=14)	Paired t-test within sequence 1 (N=14)
Mean difference between EUR-1008 and Placebo	-21.33	-20.72
95% CI	(-32.17, -10.49)	(-31.01, -10.44)
P value	<0.001	<0.001

	Placebo (Period 1) (N=17)	EUR-1008 (Period 2) (N=17)
Sequence 2 Placebo → EUR-1008		

Table A.3 T-test Results within Sequences and Periods of Coefficient of Nitrogen Absorption (CNA, %)

Mean	66.72 (3.296)	88.51 (1.531)
SD	13.591	6.311
Median	69.75	87.96
Min, Max	41.6, 93.5	73.8, 98.7

	Two independent sample t-test within sequence 2 (EUR-1008 N=17, Placebo N=17)	**Paired t-test within sequence 2 (N=17)**
Mean difference between EUR-1008 and Placebo	-21.79	-21.79
95% CI	(-29.19, -14.39)	(-28.05, -15.53)
P value	<0.001	<0.001

	Two independent sample t-test within period 1 (EUR-1008 N=15, Placebo N=17)	**Two independent sample t-test within period 2 (EUR-1008 N=17, Placebo N=14)**
Mean difference between EUR-1008 and Placebo	-19.10	-24.02
95% CI	(-26.94, -11.26)	(-34.21, -13.83)
P value	<0.001	<0.001

Source: Reviewer's Table

Table A.4 ANOVA Model Results of Coefficient of Nitrogen Absorption (CNA, %) Stratified by Placebo CNA

	EUR-1008	**Placebo**
Placebo CNA < 40	**(N=2)**	**(N=2)**
Mean (SEM)	88.82 (2.260)	37.04 (1.183)
SD	3.197	1.673
Median	88.82	37.04
Min, Max	86.6, 91.1	35.9, 38.2
LS means (SEM)	88.82 (1.804)	37.04 (1.804)
Difference between EUR-1008 and Placebo		-51.77
95% CI		(-65.47 -38.08)
P value		0.013
Placebo CNA in [40, 80]	**(N=22)**	**(N=22)**
Mean (SEM)	85.98 (1.477)	61.74 (2.457)
SD	6.929	11.524
Median	87.39	64.73
Min, Max	68.6, 95.9	40.0, 75.5
LS means (SEM)	85.53 (2.090)	61.28 (2.090)
Difference between EUR-1008 and Placebo		-24.25
95% CI		(-28.75 -19.74)
P value		<0.001

Table A.4 ANOVA Model Results of Coefficient of Nitrogen Absorption (CNA, %) Stratified by Placebo CNA

	EUR-1008	Placebo
Placebo CNA > 80	**(N=7)**	**(N=7)**
Mean (SEM)	89.76 (1.635)	86.39 (1.589)
SD	4.326	4.203
Median	89.10	84.69
Min, Max	85.2, 98.7	81.3, 93.5
LS means (SEM)	89.94 (1.682)	86.57 (1.682)
Difference between EUR-1008 and Placebo		-3.37
95% CI		(-5.49, -1.24)
P value		0.008

Source: Reviewer's Table

Table A.5 T-test Results of Coefficient of Nitrogen Absorption (CNA, %) Stratified by Placebo CNA

	Two independent sample t-test	Paired t-test
Placebo CNA < 40	**(EUR-1008 N=2, Placebo N=2)**	**(N=2)**
Mean difference between EUR-1008 and Placebo	-51.77	-51.77
95% CI	(-62.75, -40.80)	(-65.47, -38.08)
P value	0.002	0.013
Placebo CNA in [40, 80]	**(EUR-1008 N=22, Placebo N=22)**	**(N=22)**
Mean difference between EUR-1008 and Placebo	-24.25	-24.25
95% CI	(-30.03, -18.46)	(-28.75, -19.74)
P value	<0.001	<0.001
Placebo CNA > 80	**(EUR-1008 N=7, Placebo N=7)**	**(N=7)**
Mean difference between EUR-1008 and Placebo	-3.37	-3.37
95% CI	(-8.33, 1.60)	(-5.49, -1.24)
P value	0.166	0.008

Source: Reviewer's Table

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

/s/

Freda Cooner
6/9/2008 05:34:46 PM
BIOMETRICS

Mike Welch
6/9/2008 07:54:53 PM
BIOMETRICS
Concur with review.