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:	20-725 / 000	
Drug Name:	Creon (pancrelipase delayed-release 24000 unit) Capsules	
Indication(s):	Treatment of exocrine pancreatic insufficiency (PEI)	
Applicant:	Solvay Pharmaceuticals, Inc.	
Date(s):	Letter Date: June 19, 2008	PDUFA Date: Dec. 19, 2008
Review Priority:	1 Standard	
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Key Words: Clinical studies, NDA review, Cross-over Design, Data Quality

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The one submitted study provides statistically supportive evidence demonstrating the efficacy of individually dosed Creon 24000 unit capsules in patients 12 years of age or older with cystic fibrosis for treatment of maldigestion due to pancreatic exocrine insufficiency.

1.2 Background

This submission is a complete response to an approvable letter sent to the Applicant on August 16, 2007 for Creon, a pancreatic enzyme replacement therapy. The Agency deemed that the information presented was inadequate and deficiencies included lack of clinical safety and efficacy studies to support the efficacy of the intended-to-be-marketed formulation; there were also chemistry and manufacturing issues. In addition, the Division stated that "you will need to perform at least one controlled clinical trial with your intended-to-be-marketed product that demonstrates substantial evidence of clinical effectiveness of the intended-to-be-marketed product in the population intended for use (e.g., in patients with pancreatic exocrine insufficiency, such as patients with cystic fibrosis)."

The Applicant has submitted one randomized, double-blind, placebo-controlled, cross-over study (S245.3.126) to provide data to support the efficacy and safety of the to-be-marketed formulation of Creon in the treatment of pancreatic exocrine insufficiency (PEI) due to cystic fibrosis (CF) in subjects 12 years of age or older.

The Applicant's proposed indication is:

> *CREON Capsules is a pancrelipase indicated for the treatment of maldigestion in patients with exocrine pancreatic insufficiency.*

1.3 Statistical Issues and Findings

There are two statistical issues in this submission. They are: 1) one subject was re-randomized at one center (#16) after he failed to complete the second half of the crossover treatment sequence and only the data from the re-randomized occurrence was used in the analysis, and 2) one center (#23) was suspected by the Applicant to have questionable data quality. A site inspection was requested and is currently ongoing. To address these statistical issues, I conducted the primary efficacy analysis with and without these three subjects. These results did not change the efficacy conclusions of the study.

From a statistical perspective, Study S245.3.126 demonstrates a significant increase in the coefficient of fat absorption (CFA) for the Creon 24000 unit capsule, given as 4000 lipase units per gram of fat ingested, compared to placebo in patients with PEI due to cystic fibrosis.

2. INTRODUCTION

2.1 Overview

The Applicant has submitted one clinical study (S245.3.126) designed to demonstrate the safety and efficacy of the to-be-marketed formulation of CREON for the treatment of patients 12 years of age or older with maldigestion due to exocrine pancreatic insufficiency due to cystic fibrosis. Table 2.1 presents a brief summary of this study.

Table 2.1
Brief Summary of Clinical Study for CREON

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Treatment Sequence	Number Randomized (ITT[1])	Design[2]
S245.3.126 (10 / U.S.) Nov. 2007 to Mar. 2008	Patients with cystic fibrosis and confirmed pancreatic insufficiency by historical CFA less than 70% at screening	Pancrelipase / Placebo Placebo / Pancrelipase **Total**	16 (16) 16 (16) **32 (32)**	DB, R, PC, DD, CO, MC

Source: Statistical Reviewer's listing.
[1] ITT = Intent to Treat
[2] DB = Double-blind, R = Randomized, PC = Placebo Control, DD = Double-dummy, CO = Cross-over, MC = Multicenter

CREON is a pancreatic enzyme replacement therapy and according to the Applicant:

> Pancreatic enzyme replacement therapy is critical to achieving optimal growth in patients with CF due to pancreatic insufficiency and consequent malabsorption. In patients with CF, mucus blocks the pancreatic duct in the pancreas, as it does in the lungs. The pancreatic digestive enzymes are not secreted into the intestine, which inhibits the digestion of starch, fat and protein. This results in steatorrhea, abdominal pain, and weight loss resulting in poor growth. (Section 3, page 19 of study S245.3.126 report)

The previous cycle of this NDA did not provide statistically supportive evidence demonstrating the efficacy of 1) either the 3.0 g/day or the 1.5 g/day dose of Creon in adults with chronic pancreatitis or pancreatectomy or 2) individually dosed Creon in children with cystic fibrosis for treatment of maldigestion due to pancreatic exocrine insufficiency. In addition, the Creon formulation used in the studies was not shown to be bioequivalent to the intended to-be-marketed formulation.

The approvable letter sent to the Applicant on August 16, 2007 stated that an additional controlled clinical trial with the intended to-be-marketed product in patients with pancreatic exocrine insufficiency, such as patients with cystic fibrosis, needed to be conducted and demonstrate substantial evidence of clinical effectiveness for marketing approval to be granted.

The protocol for this study S245.3.126 was reviewed under IND 47,546, Serial 110. Issues related to clarification of the definition of the primary efficacy population, the accounting for missing data, clarification of the primary efficacy endpoint within the protocol, and clarification of the sample size derivation were identified and subsequently addressed which resulted in a protocol that was acceptable from a statistical perspective.

2.2 Data Sources

The study report and additional information for this study were submitted electronically. The submitted SAS data sets for the study were complete and well documented. These items are located in the Electronic Document Room at \\Fdswa150\nonectd\N20725\N_000 under submission dates 6-19-2008 and 8-12-2008.

3. STATISTICAL EVALUATION

3.1 Design of Study S245.3.126

This was a multi-center, randomized, double-blind, placebo-controlled, double-dummy, cross-over study to demonstrate the efficacy and safety of Creon (pancrelipase) 24000 unit capsules versus placebo in patients with pancreatic exocrine insufficiency (PEI) due to cystic fibrosis.

After screening, eligible subjects underwent a period of up to 14 days on their usual pancreatic enzyme supplementation at their individual dose until the next visit. At this next visit, subjects were randomized to the treatment sequence of pancrelipase/placebo or placebo/pancrelipase, hospitalized, and treated with study medication for 5 days. All food consumed was provided by the nutritional service of the investigational unit. Stool collection and dietary recording was done for 3 days (first stool dye marker is taken the evening of Day 2 of the first cross-over period; the second stool marker was taken the evening of Day 5 of the first cross-over period). Complete stool collection and dietary record was done from the first appearance of the dyed stool until the next appearance of the dyed stool for the evaluation of the coefficient of fat absorption (CFA) and coefficient of nitrogen absorption (CNA). The subject was released from the center after the last dyed stool is passed (Day 6 or 7 of the first cross-over period, depending on the GI motility of the subject.) From Day 6 of the first cross-over period onwards, the subject was released from the hospital and takes their usual enzyme supplementation.

After the first cross-over period, a wash-out period of 3 to 14 days on the subject's individual pancreatic enzyme supplementation was done until the start of the second cross-over period. On the first day of the second cross-over period, subjects were hospitalized and follow the same regimen as in the first cross-over period.

The pancrelipase dose for each subject was 4000 lipase units/g fat intake. The calculated number of capsules per day was given in divided doses according to the fat content of each meal and snack. On Days 3-5 of both cross-over treatment periods the same diet was given to the subject.

The primary efficacy objective is to show the superiority of pancrelipase over placebo in improving fat digestion. The primary endpoint is the change in the coefficient of fat absorption (CFA) and is defined as:

$$\frac{[\text{Pancrelipase fat intake} - \text{Pancrelipase fat excretion}] \times 100}{\text{Pancrelipase fat intake}} - \frac{[\text{Placebo fat intake} - \text{Placebo fat excretion}] \times 100}{\text{Placebo fat intake}}$$

The primary analysis uses an analysis of variance (ANOVA) model with sequence, period, and treatment as fixed effects and subject within sequence as random. A model-based estimate of the treatment difference along with a 95% confidence interval and p-value for testing the superiority of pancrelipase to placebo are presented. A similar analysis is performed for the CNA.

The clinically relevant difference in CFA to be detected between pancrelipase and placebo was 14% with a standard deviation of 20%. A sample size of 24 had 90% power to detect an effect size of 0.7 (14%/20%) using a paired t-test with a 0.05 two-sided level of significance. To account for drop-outs, 26 subjects (13 per treatment sequence) were planned to be randomized.

A descriptive analysis of the secondary endpoint for the change in the coefficient of nitrogen absorption (CNA) is presented by request of the Clinical Reviewer to provide evidence suggestive of the clinical utility of the protease to improve amino-acid absorption/nitrogen balance in patients with PEI treated with supplementary digestive proteases. The CNA is similarly defined as CFA, except that fat is replaced with nitrogen. Since no accounting for this endpoint in the overall study significance level was prespecified in the protocol, this information will not be used for labeling claims.

3.2 Evaluation of Efficacy for Study S245.3.126

There are two statistical issues in this submission. They are: 1) one subject was re-randomized at Center 16 after he failed to complete the second half of the crossover treatment sequence and only the data from the re-randomized occurrence was used in the analysis, and 2) Center 23 was suspected by the Applicant to have questionable data quality. According to the Applicant in section 5.8.2.2 on page 45 of the study report:

> Only the second randomization for the subject who was randomized twice was counted in the subject samples (I don't quite follow this. This subject was first randomized as Subject 1 in Center 16 but terminated the study prematurely after the first cross-over period due to a medication error (the subject took blue dye instead of study medication), see Section 6.1. The subject was randomized again as Subject 3 in Center 16 and completed the study. His data from his first randomization as Subject 1601 were included in listings only.
>
> The two subjects from Center 23 (Dr. Steinmetz) were included in the safety sample and the FA sample. The subjects were included in all analyses, i.e. efficacy and safety. Due to the questionable data quality at the center, a modified FA sample was defined which included all subjects who were in the FA sample and were from a center other than Center 23. …

According to the Clinical Reviewer from information supplied by the Sponsor:

> Site 23 was non-compliant with the calculated and administered dose for both patients. The two patients from this site were dosed according to the investigator's judgment rather than by pre-specified dose, and the pre-specified meal plan was not provided. The following additional issues were noted: adverse events recorded by ancillary study staff were not assessed during the course of the study by the PI; lack of documentation of delegated responsibilities; lack of confirmation of review of source documentation; lack of uniform source documentation at the site—there were three types of source documentation; and recordation "discrepancies" (not otherwise defined) in all three types of source documents.

Based on these issues, a site inspection was requested and is currently ongoing.

To address these statistical issues, I conduct primary efficacy sensitivity analyses using the second randomization of the subject from Center 16 and without the two subjects from Center 23.

A missing CFA/CNA value in one cross-over period was replaced by the CFA/CNA value of the other cross-over period. All subjects had CFA and CNA values in both periods except subject 0031-00002, who received pancrelipase but prematurely terminated the study and did not have stool analysis for either CFA or CNA performed in either period. Because of the data quality issues with Center 23, the Applicant also ran analyses with and without the two subjects from this center.

3.2.1 Subject Disposition and Baseline Characteristics

A total of 35 subjects consented to enroll in the study, of which there were 34 unique subjects (one subject was re-randomized after premature discontinuation from the first cross-over period). Of these 34 unique subjects, two were screen failures. The Full Analysis (FA) population had a total of 32 subjects, 16 subjects randomized to the placebo/pancrelipase treatment sequence group and 16 to the pancrelipase/placebo treatment sequence group. Demographic and baseline characteristics for both treatment sequence groups were similar with a mean age of 22 years and the majority being Caucasian (>93%) and male (>56%). The study discontinuation rate for each group is 0% in the placebo/pancrelipase sequence group and 6.3% (1 of 16) in the pancrelipase/placebo sequence group. The single pancrelipase/placebo sequence group subject discontinuation is due to an adverse event that occurred one day after taking all pancrelipase treatment during the first cross-over period. This subject did not have any of their stool samples analyzed for fat and nitrogen content, therefore, this data is not available.

3.2.2 Efficacy Results

The Applicant's result for the primary efficacy endpoint of change in CFA is presented in Table 3.1. The one re-randomized subject from Center 16 received placebo study treatment in cross-over period 1 but prematurely terminated after the first randomization. He completed the study after their second randomized and this data is used for this analysis. I concur with the Applicant's results. Specifically, the CFA increases by a mean of 39.0% ($p<0.001$) when using pancrelipase compared to placebo.

Table 3.1
Study S245.3.126: Change in CFA (%) for ITT Population

	Pancrelipase	Placebo	Pancrelipase - Placebo
n	31	31	
Sample Mean (s.d.)	88.6 (6.6)	49.8 (18.3)	
Adjusted Mean (s.e.)	88.6 (2.3)	49.6 (2.3)	
Adjusted Mean Treatment Difference vs. Placebo (95% C.I.)			39.0 (32.3, 45.8)
p-value for Adjusted Mean Treatment Difference			<0.001

Source: Table 9 on page 54 of Study S245.3.126 report.
Adjusted mean estimates are based on an ANOVA model with treatment, sequence, and period as fixed effects and subject within sequence as a random effect.

The Applicant's result for the secondary endpoint of change in CNA is presented in Table 3.2. I concur with the Applicant's descriptive results. Specifically, the CNA increases by a mean of 35.2% (95% C.I. from 29.6% to 40.8%) when using pancrelipase compared to placebo.

Table 3.2
Study S245.3.126: Change in CNA (%) for ITT Population

	Pancrelipase	Placebo	Pancrelipase - Placebo
n	31	31	
Sample Mean (s.d.)	85.1 (6.4)	50.0 (17.1)	
Adjusted Mean (s.e.)	85.1 (1.9)	49.9 (1.9)	
Adjusted Mean Treatment Difference vs. Placebo (95% C.I.)			35.2 (29.6, 40.8)

Source: Table 10 on page 55 of Study S245.3.126 report.
Adjusted mean estimates are based on an ANOVA model with treatment, sequence, and period as fixed effects and subject within sequence as a random effect.

3.2.3 Sensitivity Analyses

Sensitivity analyses for the primary efficacy endpoint of change in CFA and the secondary endpoint of change in CNA were performed.

First, an analysis using the ITT population without the two subjects from Center 23, where the data quality was in question, gave similar results to the ITT analysis. The CFA increases by a mean of 40.5% (95% C.I. from 33.7% to 47.4%, p-value<0.001) when using pancrelipase compared to placebo. The CNA increases by a mean of 36.6% (95% C.I. from 31.1% to 42.2%) when using pancrelipase compared to placebo.

Next, an analysis using the ITT population with the first randomization results for the subject from Center 16 who was re-randomized gave similar results to the ITT analysis. Since this subject did not complete the second cross-over period, the values from the first cross-over period were carried over for a null treatment effect. The CFA increases by a mean of 38.6% (95% C.I. from 31.6% to 45.7%, p-value<0.001) when using pancrelipase compared to placebo. The CNA increases by a mean of 34.7% (95% C.I. from 28.8% to 40.6%) when using pancrelipase compared to placebo.

3.3 Evaluation of Safety

There are no statistical issues with evaluation of safety. Refer to the clinical review evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

There are no adequately sized subgroups of interest to justify reasonable subgroup efficacy analyses.

5. CONCLUSIONS

For the primary efficacy analysis based on the coefficient of fat absorption, the one submitted study provides statistically supportive evidence demonstrating the efficacy of individually dosed Creon 24000 unit capsules in patients with cystic fibrosis 12 years of age or older for the treatment of maldigestion due to pancreatic exocrine insufficiency.

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/s/

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