CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
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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
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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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Concur with review.

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) Capsules
Indication(s):	Treatment of exocrine pancreatic insufficiency (PEI)
Applicant:	Solvay Pharmaceuticals, Inc.
Date(s):	Letter Date: November 17, 2006 PDUFA Date: July 27, 2007
Review Priority:	1 Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Sonia Castillo, Ph.D.
Biometrics Team Leader:	Mike Welch, Ph.D.
Medical Division:	Division of Gastroenterology Products
Clinical Team:	Ethan Hausman, M.D., Medical Reviewer Anne Pariser, M.D., Team Leader
Project Manager:	Maureen Dewey

Key Words: Clinical studies, NDA review, Interim analysis, Sample size re-estimation

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APPENDIX **9**

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The two submitted studies do 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 these studies was not shown to be bioequivalent to the to-be-marketed formulation.

1.2 Background

This submission is a complete response to a not approvable letter sent to the Applicant on October 9, 2003 for Creon, a pancreatic enzyme (?) replacement therapy. The Agency deemed that the information presented was inadequate and deficiencies included lack of data to support the use of Creon in children under age seven; there were also chemistry and manufacturing issues. However, efficacy was demonstrated for adults with pancreatic exocrine insufficiency due to chronic pancreatitis or cystic fibrosis. In addition, the Division stated that "once the chemistry deficiencies have been corrected, you will need to link the intended to-be-marketed formulation with the formulation used in the clinical trials."

In this submission, the Applicant provides data for pediatric cystic fibrosis patients under 7 years of age and data to support the use of Creon in patients who have had upper GI surgery leading to partial or total pancreatectomy. The Applicant has submitted two clinical studies, to evaluate the efficacy and safety of Creon in the treatment of pancreatic exocrine insufficiency (PEI). One study (S245.3.115) is a randomized, double-blind, placebo-controlled, parallel group study in adult subjects with PEI due to chronic pancreatitis (CP) or pancreatectomy and the other study (S248.3.003) is an open-label uncontrolled study in children with cystic fibrosis. In addition, this submission also presents information intended to link the to-be-marketed formulation with the formulation used in these two clinical trials.

According to the Applicant:

> Pancreatic exocrine insufficiency (PEI) is a serious and life-threatening condition caused by underlying diseases or conditions like chronic pancreatitis (CP), pancreatectomy, gastrectomy, cystic fibrosis (CF) and others. Subjects with PEI due to CP and CF are the best diagnosed and investigated patient groups in terms of maldigestion due to PEI. The clinical symptomatology of the disease, the need for enzyme supplementation and the therapeutic perspectives to treat maldigestion are well defined. … The symptomatology of PEI is the consequence of the lack of digestive enzymes leading to malnutrition as the main symptom. … Ultimately, PEI results in undernutrition, weight loss and failure to thrive in children. … Lipid maldigestion is the main cause of fecal energy loss leading to the major symptoms of PEI. The therapy of PEI is focusing on lipase as main enzyme. The efficacy of the lipase will be used as the main marker for efficacy of pancreatin products.
>
> Creon is an enteric-coated pellet preparation containing highly concentrated pancreatin which [is extracted from pig pancreas]. It is used in clinical practice as pancreatic enzyme supplementation for the treatment of PEI caused by chronic pancreatitis, pancreatectomy, gastrectomy or cystic fibrosis ... (Section 3, page 39 of study S245.3.115 report)

The Applicant's proposed indication is:

> *CREON Capsules is indicated for adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency.*

1.3 Statistical Issues and Findings

There are three statistical issues in this submission related to the adult PEI study (S245.3.115). The Applicant: 1) presented a secondary ANCOVA analysis as the primary analysis instead of the protocol specified ANOVA analysis, 2) used the Per Protocol population instead of the ITT population as the primary efficacy population, and 3) performed an unplanned interim analysis for adjustment of the sample size to ensure adequate power to detect a difference. For the pediatric study (S248.3.003). The lack of a control and the small sample size (n=12), did not allow for inference of efficacy results.

To address these statistical issues, in the adult study I have presented the ANOVA analysis results, used the ITT population in the primary efficacy analysis, but do not adjust the p-values to compensate for the unplanned interim analysis for sample size re-estimation. For the pediatric study, descriptive statistics are presented without reference to statistical inference and with interpretation left to the clinical reviewer.

The results for the primary efficacy endpoint of coefficient of fat absorption (CFA%) for the two studies are as follow:

- Study S245.3.115 does not demonstrate a significant increase in CFA% for either the 3.0 g/day or 1.5 g/day dose of Creon compared to placebo in adults with PEI due to chronic pancreatitis or pancreatectomy, although there is a trend in increased CFA% for both doses.
- Study S248.3.003 does not demonstrate a significant increase from baseline in CFA% for individually dosed Creon compared to placebo in children with PEI due to cystic fibrosis, although there is a trend in increased CFA%.

These results do not provide statistically significant evidence of efficacy for the 3.0 g/day or 1.5 g/day dose of Creon in adults with PEI due to chronic pancreatitis or pancreatectomy or for individually dosed Creon for children with cystic fibrosis. In addition, the Creon formulation used in these studies has not been shown by the Applicant to be bioequivalent to the to-be-marketed formulation (see Biopharm review).

2. INTRODUCTION

2.1 Overview

The Sponsor has submitted two clinical studies (S245.3.115 and S248.3.003) designed to demonstrate the safety and efficacy of CREON for the treatment of adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency. Table 2.1 presents a brief summary of each of the two studies addressed in this review.

There are three statistical issues in this submission. They are: 1) the Applicant presenting a secondary ANCOVA analysis as the primary analysis instead of the protocol specified ANOVA analysis, 2) using the Per Protocol population instead of the ITT population as the primary efficacy population, and 3) performing an unplanned interim analysis for adjustment of the sample size to ensure adequate power to detect a difference.

My review presents for the adult study, the Applicant's primary efficacy analyses based on the ANOVA analysis using the ITT population with no statistical inference concerning significance tests (to address the unplanned interim analysis for sample size re-estimation). And for the pediatric study, my review presents descriptive statistics without reference to statistical inference and with interpretation left to the clinical reviewer.

Table 2.1
Brief Summary of Clinical Studies for CREON

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Treatment	Number Randomized (ITT[1])	Design[2]
S245.3.115 (32 / Japan) June 2000 to June 2003	Adult patients with chronic pancreatitis or who had a pancreatectomy, and who had at least 7.5 g/day of stool fat excretion at screening	Creon 1.5 g/day Creon 3.0 g/day Placebo **Total**	31 (30) 33 (33) 30 (30) **94 (93)**	DB, R, PC, DD, PG, MC
S248.3.003 (2 / Italy) June 2002 to Sept. 2004	Children aged 1 to 24 months with diagnosis of cystic fibrosis and pancreatic insufficiency, and a CFA less than 70% at screening	Creon (dosed as 2000 lipase units/g of fat intake) **Total**	12 (12) **12 (12)**	OL, NC, MC

Source: Statistical Reviewer's listing.
[1] ITT = Intent to Treat
[2] DB = Double-blind, R = Randomized, PC = Placebo Control, DD = Double-dummy, PG = Parallel Group, MC = Multicenter, OL = Open-label, NC = Noncomparative

2.2 Data Sources

The study reports and additional information for these studies were submitted electronically. The submitted SAS data sets for all studies were complete and well documented. These items are located in the Electronic Document Room at \\Cdsesub1\EVSPROD\N20725\N_000 under submission dates 11-17-2006, 2-6-2007, and 3-12-2007.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy for Study S245.3.115

This is a multi-center, randomized, double-blind, placebo-controlled, parallel group study to demonstrate the efficacy and safety of Creon 3.0 g/day versus placebo in patients with pancreatic exocrine insufficiency (PEI) due to chronic pancreatitis or pancreatectomy. Eligible subjects were randomized in a 1:1:1 ratio to receive a specific oral dose of placebo, Creon 1.5 g/day, and Creon3.0 g/day in a double-dummy fashion as 2 sachets per dosing for three doses per day as follows:

- Creon 3.0g/day receives 2 Creon 0.5-g sachets
- Creon 1.5g/day receives 1Creon 0.5-g sachet and 1 Placebo 0.5-g sachet
- Placebo receives 2 Placebo 0.5-g sachets

The study period consisted of a 5-day placebo run-in phase and a 7-day randomized treatment phase, which were conducted under hospitalization. Subjects had at least 40 g/day of fat intake through the run-in and the treatment phases. Stool collection was done for one day at screening to confirm that subjects have at least 7.5 g/day of stool fat excretion. Stool collection during the run-in phase was done for the last 3 days (from morning of day 3 until first defecation on day 6), and during the treatment phase is done for the last 3 days (from morning of day 10 until first defecation on day 13); from which stool fat excretion and stool frequency were assessed.

The primary objective is to demonstrate the efficacy of Creon 3.0 g/day in patients with pancreatic exocrine insufficiency (PEI) caused by chronic pancreatitis or by pancreatectomy as compared to placebo based on the change in the CFA%.

The primary endpoint is the change from baseline in the coefficient of fat absorption (CFA%), which is defined as:

$$\frac{[\text{Treatment fat intake} - \text{Treatment fat excretion}] \times 100}{\text{Treatment fat intake}} - \frac{[\text{Baseline fat intake} - \text{Baseline fat excretion}] \times 100}{\text{Baseline fat intake}}$$

Both fat intake and fat excretion are in units of g/day.

A supportive analysis of Creon 1.5 g/day for the change from baseline in CFA% and subgroup analyses by diagnosis (chronic pancreatitis and pancreatectomy) were specified in the protocol and are presented. By request of the Clinical Reviewer, additional analyses of stool frequency, caloric intake, and primary efficacy analyses based on the Per Protocol population are presented in the Appendix (Tables A.1, A.2, and A.3) but not addressed in the body of this review.

The protocol specified primary efficacy population is the Per Protocol population, which is not appropriate. Instead I will use and present efficacy analysis based on the Intent-to-Treat population, defined as all randomized subjects who took at least one dose of study medication. The Per Protocol population had a total of 63 subjects (20 placebo, 20 Creon 1.5 g/day, and 23 Creon 3.0 g/day) and the ITT population had a total of 93 subjects (30 placebo, 30 Creon 1.5 g/day, and 33 Creon 3.0 g/day).

The primary analysis uses an analysis of variance (ANOVA) model with treatment as the factors for comparison between each Creon group and placebo for the change from baseline in the CFA%. Testing is done using a two-sided t-test at the 5% significance level based on the ANOVA model

The protocol specified sample size was 18 subjects per treatment arm and remained at this size through four protocol amendments dated 7-28-2000, 1-16-2001, 9-11-2001, and 5-24-2002. Then, in the 8-6-2002 protocol

amendment, the sample size was changed to 25 subjects per treatment arm to ensure 20 evaluable subjects for analysis. The justification given for the change in sample size given in the protocol is:

> Simulation was performed using the number of patients eligible for the efficacy evaluation at the end of May 2002, in order to check on mean and standard deviation, and it was determined: that the original sample size is too small to ensure a power of 90% at a significance level of 5%; the required sample size is from 17 to 26 per group. Based on a feasibility analysis it has been decided to recruit 20 patients.

I requested additional information documenting the interim sample size adjustment; however the information provided was not adequate to determine the rationale and procedures for this unplanned analysis, and it appears the analysis was unblinded. Consequently, the reported p-values for the final analyses are not interpretable, and there is no formal statistical adjustment that can be applied. The interim analysis was applied to 41 evaluable subjects that included 25 pancreatectomy subjects and 16 chronic pancreatitis subjects.

3.1.1 Overall Descriptive Statistics for Study S245.3.115

For the ITT population, demographic and baseline characteristics are comparable among the treatment groups. The subject's mean age is greater than 60 years, all subjects are Japanese, and the majority are male (>75%). The number of pancreatectomy subjects is 58 and of pancreatitis subjects is 35.

3.1.2 Results for Study S245.3.115

The Applicant's results for the change in CFA% for all patients (the primary analysis) and by diagnosis (subgroup analysis) are presented in Table 3.1 below. I concur with the Applicant's results.

Table 3.1
Study S245.3.115: Change in CFA (%) for All Patients and by Diagnosis for ITT Population

	Creon 1.5 g/day	Creon 3 g/day	Placebo
Overall			
n	30	33	30
Baseline mean (%)	67.2	67.9	54.8
Mean change from baseline (%)	10.9	15.5	3.9
Mean Treatment Difference vs. Placebo (s.e.)	7.1 (4.8)	11.6 (4.7)	
p-value for Mean Treatment Difference	0.144	0.015	
Chronic Pancreatitis			
n	11	12	12
Baseline mean (%)	69.8	77.9	56.7
Mean change from baseline (%)	8.9	7.0	5.4
Mean Treatment Difference vs. Placebo (s.e.)	3.5 (5.7)	1.6 (5.6)	
p-value for Mean Treatment Difference	0.540	0.781	
Pancreatectomy			
n	19	21	18
Baseline mean (%)	65.8	62.2	53.5
Mean change from baseline (%)	12.1	20.4	2.8
Mean Treatment Difference vs. Placebo (s.e.)	9.2 (6.8)	17.5 (6.6)	
p-value for Mean Treatment Difference	0.180	0.011	

Source: Table 17 on page 88, Table 19 on page 90, Table 33 on page 100, and Table 34 on page 101 of Study S245.3.115 report and Statistical Reviewer's Analysis. Results based on ANOVA model with treatment as factor.

The statistical significance of the comparisons between Creon 3.0 g/day and Creon 1.5 g/day compared to placebo are not interpretable because of the unplanned interim analysis to increase sample size (see section 3.1). Descriptively, the following is noted:

- For all subjects, Creon 3.0 g/day had a 11.6% increase in CFA compared to placebo and Creon 1.5 g/day had a 7.1% increase in CFA compared to placebo.
- For the chronic pancreatitis subjects, Creon 3.0 g/day had a 1.6% increase in CFA compared to placebo and Creon 1.5 g/day had a 3.5% increase in CFA compared to placebo.

- For the pancreatectomy subjects, Creon 3.0 g/day had a 17.5% increase in CFA compared to placebo and Creon 1.5 g/day had a 9.2% increase in CFA compared to placebo.

In addition, the overall increase in CFA seen for each dose group is driven by the results for the pancreatectomy subjects, with a small contribution from the chronic pancreatitis subjects.

3.2 Evaluation of Efficacy for Study S248.3.003

This is a multi-center, open-label, single-arm study to demonstrate the efficacy and safety of Creon in infants with pancreatic insufficiency (PEI) due to cystic fibrosis (CF). No placebo arm was included for ethical reasons because pancreatic replacement therapy is standard therapy in PEI due to CF. Each subject received an individual Creon dose of 2000 lipase units based on their dietary per gram fat intake. Subjects' parents kept a daily diary where they recorded study medication intake, stool frequency, and other gastrointestinal information.

The study period lasted 8 weeks but for efficacy purposes the time of interest consisted of a 10-day screening (baseline) phase and the first 14-day treatment phase, which were conducted under hospitalization. At screening, the diagnosis of CF and PEI was confirmed. Baseline CFA was determined from the 72-hour stool collection from the last three days during the 10-day screening period. The final assessment of CFA was determined from the 72- hour stool collection from the last three days of the first two-week treatment period. Dietary fat intake was calculated from total fat intake during the stool collection phase. Subjects received food without fat or food with known fat content. Fat was added so that fat intake was approximately 3 g/kg body weight. The first and last meal was marked by administering a dye immediately before the meal so that stools corresponding to the dietary assessments could be identified.

The primary study objective is to demonstrate the efficacy of Creon in infants with PEI due to cystic fibrosis based on the treatment CFA% compared to baseline CFA% after 2 weeks of treatment. The primary endpoint is the change from baseline in the coefficient of fat absorption (CFA%), which is defined as:

$$\frac{[\text{Treatment fat intake} - \text{Treatment fat excretion}] \times 100}{\text{Treatment fat intake}} - \frac{[\text{Baseline fat intake} - \text{Baseline fat excretion}] \times 100}{\text{Baseline fat intake}}$$

Both fat intake and fat excretion are in units of g/day.

By request of the Clinical Reviewer: 1) supportive analyses for CFA that stratify patients by baseline CFA < 60% and CFA ≥60% are presented in the results section; and 2) additional analyses of stool frequency, change in BMI, and weight-for-Height are presented in the Appendix (Table A.4) but not addressed in the body of this review.

The protocol specified primary efficacy population is the Intent-to-Treat (ITT) population, defined as all subjects who took at least one dose of study medication and provide some efficacy data after 2 weeks of treatment.

The primary analysis uses a two-sided, paired t-test at the 5% significance level to test that the mean CFA% change from baseline is equal to zero. Means and 95% confidence intervals are presented below.

The protocol specified sample size, accounting for drop-outs, was 12 subjects to allow for 10 evaluable subjects.

3.2.1 Overall Descriptive Statistics for Study S248.3.003

For the ITT population, demographic and baseline characteristics are as follow: the mean age was 12 months, all subjects were Caucasian, and seven were female (58.3%). All 12 ITT subjects completed the study.

3.2.2 Results for Study S248.3.003

The Applicant's results for the change in CFA% for all patients (the primary analysis) and my results for the change in CFA% by baseline CFA category (exploratory subgroup analysis) are presented in Table 3.2 below. I concur with the Applicant's results.

Table 3.2
Study S248.3.003: Change in CFA (%) by Baseline CFA (%) Category for ITT Population

	All Subjects	Baseline CFA<60%	Baseline CFA≥60%
n	12	4	8
Baseline mean (%)	58.0	41.4	66.4
Mean change from baseline (95% C.I.)	26.7 (12.9, 40.4)	42.6 (-0.9, 86.1)	18.7 (6.8, 30.6)

Source: Table 7 on page 42 of Study S248.3.003 report and Statistical Reviewer's analysis

Descriptively, the following results are noted:

- For all subjects, the CFA increased by a mean of 26.7% (95% C.I. from 12.9% to 40.4%) compared to baseline
- For subjects whose baseline CFA is less than 60%, the CFA increased by a mean of 42.6% (95% C.I. from -0.9% to 86.1%) compared to baseline
- For subjects whose baseline CFA is greater than or equal to 60%, the CFA increased by a mean of 18.7% (95% C.I. from 6.8% to 30.6%) compared to baseline

3.3 Evaluation of Safety

There is no statistical evaluation of safety necessary for this review. For information, reference the clinical review evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

The subgroups of interest in this submission are 1) the chronic pancreatitis and pancreatectomy subjects in the adult study and 2) those pediatric subjects with a CFA < 60% or with a CFA ≥ 60% at baseline. These results are presented in sections 3.1.2 and 3.2.2, respectively.

5. CONCLUSIONS

For the primary efficacy analysis based on the coefficient of fat absorption (CFA%), the two submitted studies do 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 these studies was not determined to be bioequivalent to the to-be-marketed formulation.

APPENDIX

Table A.1
Study S245.3.115: Change in Number of Stools per Day for All Patients and by Diagnosis for ITT Population

	Creon 1.5 g/day	Creon 3 g/day	Placebo
Overall			
n	30	33	30
Baseline mean	2.0	1.8	2.4
Mean change from baseline	-0.08	-0.11	-0.07
Mean Treatment Difference vs. Placebo (s.e.)	-0.01 (0.20)	-0.04 (0.19)	
p-value for Mean Treatment Difference	0.955	0.819	
Chronic Pancreatitis			
n	11	12	12
Baseline mean	1.9	2.1	2.3
Mean change from baseline	-0.12	0.03	-0.42
Mean Treatment Difference vs. Placebo (s.e.)	0.29 (0.33)	0.44 (0.33)	
p-value for Mean Treatment Difference	0.382	0.182	
Pancreatectomy			
n	19	21	18
Baseline mean	2.0	1.7	2.4
Mean change from baseline	-0.05	-0.19	0.17
Mean Treatment Difference vs. Placebo (s.e.)	-0.22 (0.24)	-0.36 (0.24)	
p-value for Mean Treatment Difference	0.367	0.135	

Source: Statistical Reviewer's Analysis based on ANOVA model with treatment as factor.

Table A.2
Study S245.3.115: Change in Caloric Intake (kcal/day) for All Patients and by Diagnosis for ITT Population

	Creon 1.5 g/day	Creon 3 g/day	Placebo
Overall			
n	30	33	30
Baseline mean (kcal/day)	1949.7	1987.4	1958.7
Mean change from baseline (kcal/day)	10.6	-62.0	-6.2
Mean Treatment Difference vs. Placebo (s.e.)	16.7 (40.7)	-55.9 (39.8)	
p-value for Mean Treatment Difference	0.682	0.164	
Chronic Pancreatitis			
n	11	12	12
Baseline mean (kcal/day)	1976.6	2047.7	2002.2
Mean change from baseline (kcal/day)	16.9	-44.1	-43.7
Mean Treatment Difference vs. Placebo (s.e.)	60.6 (48.1)	-0.4 (47.0)	
p-value for Mean Treatment Difference	0.217	0.993	
Pancreatectomy			
n	19	21	18
Baseline mean (kcal/day)	1934.1	1952.9	1929.7
Mean change from baseline (kcal/day)	6.9	-72.3	18.8
Mean Treatment Difference vs. Placebo (s.e.)	-11.9 (59.1)	-91.1 (57.7)	
p-value for Mean Treatment Difference	0.841	0.120	

Source: Statistical Reviewer's Analysis based on ANOVA model with treatment as factor.

Table A.3
Study S245.3.115: Change in CFA (%) for All Patients and by Diagnosis for Per Protocol Population*

	Creon 1.5 g/day	Creon 3 g/day	Placebo
Overall			
n	20	23	20
Baseline mean (%)	58.1	61.5	46.2
Mean change from baseline (%)	14.6	20.4	8.4
Mean Treatment Difference vs. Placebo (s.e.)	6.2 (6.4)	12.0 (6.2)	
p-value for Mean Treatment Difference	0.332	0.055	
Chronic Pancreatitis			
n	8	6	9
Baseline mean (%)	65.5	70.6	50.5
Mean change from baseline (%)	10.2	11.7	8.7
Mean Treatment Difference vs. Placebo (s.e.)	1.5 (7.5)	3.0 (8.1)	
p-value for Mean Treatment Difference	0.843	0.710	
Pancreatectomy			
n	12	17	11
Baseline mean (%)	53.2	58.3	42.7
Mean change from baseline (%)	17.6	23.5	8.1
Mean Treatment Difference vs. Placebo (s.e.)	9.4 (9.4)	15.3 (8.7)	
p-value for Mean Treatment Difference	0.322	0.086	

Source: Statistical Reviewer's Analysis based on ANOVA model with treatment as factor.
* Per Protocol population: subjects who met all the inclusion and none of the exclusion criteria, have assessment data after start of study treatment, and did not fall under any of 11 pre-specified categories for cases to be excluded from the efficacy analysis.

Table A.4
Study S248.3.003: Change in BMI, Weight for Height, and Number of Stools per Day for ITT Population (n=12)

Parameter	
BMI (kg/m^2)	
Baseline mean	15.7
Mean change from baseline (95% C.I.)	0.3 (-0.1, 0.8)
Weight for Height (%)	
Baseline mean	99.3
Mean change from baseline (95% C.I.)	0.7 (-3.8, 5.1)
Number of Stools per Day	
Baseline mean	2.9
Mean change from baseline (95% C.I.)	-0.6 (-1.2, 0.01)

Source: Table 13 on page 48 and Table 16 on page 50 of Study S248.3.003 report and Statistical Reviewer's analysis.

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/s/

Sonia Castillo
7/17/2007 01:31:47 PM
BIOMETRICS

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Concur with review.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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OFFICE OF BIOSTATISTICS
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STATISTICAL REVIEW AND EVALUATION

NDA:	20-725
DATE RECEIVED BY CENTER:	July 31, 1997
DRUG NAME:	Creon® Minimicrospheres® (Pancrelipase Delayed-Release Capsules, USP)
INDICATION:	Treatment of adult and pediatric patients with exocrine pancreatic insufficiency
SPONSOR:	Solvay Pharmaceuticals
DOCUMENT REVIEWED:	Volumes 1, 2, and 70 to 119 dated July 31, 1997.
STATISTICAL REVIEWER:	Wen-Jen Chen, Ph.D. (HFD-715)
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STATISTICAL KEYWORDS: Clinical studies; NDA review.

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1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Overview of Clinical Program and Studies Reviewed

The sponsor submitted four-phase III studies, CR200.0126, CR200.0143, CR200.0124, and K.245.5005 (protocol number) to support the use of Creon® Minimicrospheres Capsules to treat adult and pediatric patients with exocrine pancreatic insufficiency. Of the four studies, the sponsor indicated that the three studies CR200.0126, CR200.0143, and CR200.0124 were considered as pivotal studies while the other one K.245.5005 was supportive. However, for the study with protocol number K.245.5005, the sponsor further indicated that the overall conduct of the study and the verification of the source documentation for the essential data elements generated in the study were doubted by US and European Solvary Pharmaceuticals Compliance Audit. As a result, the remaining three main studies CR200.0126, CR200.0143, and CR200.0124 are the focus of this review.

Of the three studies, the two Studies CR200.0126 and CR200.0143 were for the treatment of steatorrhea in patients with cystic fibrosis while Study CR200.0124 was for the treatment of steatorrhea in patients with chronic pancreatitis. Furthermore, Study CR200.0126 recruited pediatric and adolescent patients with ages from 7 to 18 years while Studies CR200.0143 and CR200.0124 enrolled adults (ages ≥ 18).

Noted by this reviewer, Solvay Pharmaceuticals, Inc. was placed under the Application Integrity Policy (AIP) on September 24, 1997 and review of the NDA was suspended. On April 9, 2003, the AIP was revoked for Solvay Pharmaceuticals, Inc. and the time frame for review restarted as of the date the AIP was revoked.

1.2 Principal Findings

1.2.1 Study CR200.0126

- The ANCOVA analysis using CFA at the end of double blind phase as the dependent variable along with the treatment effect, center, treatment by center, and baseline CFA as the explanatory variables, performed by this reviewer, shows that Creon®20 is superior to placebo. It indicates that the superiority of Creon®20 to placebo is not sensitive to the different analysis model.
- Although the mean change in CFA for placebo in center 1 is much smaller than that of other centers, the superiority of Creon®20 to placebo still holds using patients excluding center 1. As a result, the superiority of Creon®20 to placebo is not dominated by centers with unusual data.

1.2.2 Study CR200.0143

- The effect of Creon®20 is consistently better than that of placebo across the five centers assessed by the change in CFA from the open label phase to the double-blind phase. The significant interaction between treatment and center is deemed as a quantitative interaction. Thus, the treatment efficacy comparison can be performed by pooling/averaging the differences of the treatment effects across the centers. The results from the sponsor's unweighted and this reviewer's weighted methods all show that the efficacy of Creon®20 is significantly better than that of placebo assessed by the change in CFA from the open-label phase to the double-blind treatment phase.
- The ANCOVA analysis using CFA at the end of the double blind phase as the dependent variable along with treatment effect, center, treatment by center, and baseline CFA as the explanatory variables, performed by this reviewer, shows that Creon®20 is superior to placebo. It indicates that the superiority of Creon®20 to placebo is not sensitive to the different analysis model.

1.2.3 Study CR200.0124

- Noted by this reviewer, only one main study was submitted by the sponsor to support the use of Creon®10 on fat absorption for patients with exocrine pancreatic insufficiency caused by chronic pancreatitis. For a single study concluded adequate in support of an effectiveness claim, the guidance for industry (1998) "Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" indicates that the presence of one or more of the following five characteristics in the study can contribute to that conclusion: 1.) Large multi-center study, 2.) Consistency across study subsets, 3.) Multiple studies in a single study, 4.) Multiple endpoints involving different events, and 5.) Statistically very persuasive finding. For item 5, the Guidance emphasizes that in a multi-center study, a very low p-value (for example, less than .00125) indicates the result is highly inconsistent with the null hypothesis of no treatment effect. Thus, for a single study to be considered statistically persuasive in support of the efficacy claim, the p-value for the treatment comparison should be very small, like less than .00125. Clearly, although at the significance level of .05, the effectiveness of Creon®10 is significantly better than that of placebo after excluding the Creon patient with abnormal CFA change value 122, the two p-values 0.023 and 0.03 for the treatment comparisons, calculated respectively using the sponsor's general linear model and the Mann-Whitney-Wilcoxon rank test, are not low, assessed based on one single study with small sample size of 25. Finally, based on the trial design and the statistical analysis results, none of the five characteristics is found in this study. As a result, in the light of the guidance for industry (1998), the superiority of Creon®10 to placebo assessed by the change in CFA from the single blind placebo phase to the double blind treatment phase is not statistically persuasive.
- From the statistical perspective, the single study did not provide substantial evidence to support the use of Creon®10 on fat absorption for patients with exocrine pancreatic insufficiency caused by chronic pancreatitis. However, it is the medical reviewer's

decision to consider the capability of adopting the efficacy results shown in the support of using Creon®20 for the cystic fibrosis patients to support the use of Creon®10 to treat the patients with exocrine pancreatic insufficiency associated with chronic pancreatitis.

1.3 Conclusions and Recommendations

From the sponsor's analysis results and the finding remarks of the two Studies CR200.0126 and CR200.0143, the Overall Conclusions and Recommendations on the efficacy of study drug Creon®20 in treatment of patients with exocrine pancreatic insufficiency associated with cystic fibrosis disease are made as follows:

- The efficacy of Creon®20 is superior to that of placebo as assessed by the change in CFA from the open label phase to the double-blind phase. This efficacy is not sensitive to the different analysis model.
- Study CR200.0126 indicates that although the mean change in CFA for placebo in center 1 is much smaller than that of other centers, the superiority of Creon®20 to placebo still holds using patients excluding center 1. Thus, the superiority of Creon®20 to placebo is not dominated by centers with unusual data.
- Study CR200.143 indicates that the effect of Creon®20 is consistently better than that of placebo across the five centers assessed by the change in CFA from the open label phase to the double-blind phase. The significant interaction between treatment and center is deemed as a quantitative interaction. Thus, the treatment efficacy comparison can be performed by pooling/averaging the differences of the treatment effects across the centers. The results from the sponsor's unweighted method and this reviewer's weighted method all show that the efficacy of Creon®20 is significantly better than that of placebo assessed by the change in CFA from open-label to double-blind treatment phase.
- As a consequence, the efficacy of study drug Creon®20 in treatment of patients with exocrine pancreatic insufficiency associated with cystic fibrosis disease is superior to that of placebo.

From the finding remarks of Study CR200.0124, the Overall Conclusions and Recommendations on the efficacy of study drug Creon®10 in treatment of patients with exocrine pancreatic insufficiency associated with chronic pancreatitis disease are made as follows:

- Noted by this reviewer, only one main study was submitted by the sponsor to support the use of Creon®10 on fat absorption for patients with exocrine pancreatic insufficiency caused by chronic pancreatitis. For a single study concluded adequate in support of an effectiveness claim, the guidance for industry (1998) "Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" indicates that the presence of one or more of the following five characteristics in the study can contribute to that conclusion: 1.) Large multi-center study, 2.) Consistency across study subsets, 3.) Multiple studies in a single study, 4.) Multiple endpoints involving different events, and 5.) Statistically very persuasive finding. For item 5, the Guidance emphasizes that in a multi-center study, a very low p-value (for example, less than .00125) indicates

the result is highly inconsistent with the null hypothesis of no treatment effect. Thus, for a single study to be considered statistically persuasive in support of the efficacy claim, the p-value for the treatment comparison should be very small, like less than .00125. Clearly, although at the significance level of .05, the effectiveness of Creon®10 is significantly better than that of placebo after excluding the Creon patient with abnormal CFA change value 122, the two p-values 0.023 and 0.03 for the treatment comparisons, calculated respectively using the sponsor's general linear model and the Mann-Whitney-Wilcoxon rank test, are not low, assessed based on one single study with small sample size of 25. Finally, based on the trial design and the statistical analysis results, none of the five characteristics is found in this study. As a result, in the light of the guidance for industry (1998), the superiority of Creon®10 to placebo assessed by the change in CFA from the single blind placebo phase to the double blind treatment phase is not statistically persuasive.

- From the statistical perspective, the single study did not provide substantial evidence to support the use of Creon®10 on fat absorption for patients with exocrine pancreatic insufficiency caused by chronic pancreatitis. However, it is the medical reviewer's decision to consider the capability in adopting the efficacy results shown in the support of using Creon®20 for the cystic fibrosis patients to support the use of Creon®10 to treat the patients with exocrine pancreatic insufficiency associated with chronic pancreatitis.

2.0 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

In this NDA submission, the sponsor made the following observations with regard to Creon:

> Creon® Minimicrospheres® Capsules contain pancrelipase, a digestive enzyme product porcine pancreatic origin. The pancreatic enzymes (lipase, protease, amylase) in Creon® Minimicrospheres® Capsules aid in food digestion by catalyzing the hydrolysis of fat to monoglycerol, glycerol and fatty acids, protein into peptides and amino acids, and starch into dextrins and short chain sugars. The Minimicrospheres® formulation includes Creon® 5, Creon® 10, Creon® 20 Capsules, which are identical to each other in formulation but vary only in the quantity of Minimicrospheres® used to create the different enzyme strengths.
>
> Pancreatic enzyme supplements form the cornerstone in the treatment of steatorrhea and malabsorption associated with exocrine pancreatic insufficiency. Creon® Minimicrospheres® Capsules are indicated for adults and children with exocrine pancreatic insufficiency (EPI) as is often associated with, but not limited to: cystic fibrosis (CF), chronic pancreatitis (CP), postpancreatectomy, postgastrointestinal bypass surgery, and ductal obstruction of the pancreas or common bile duct.

The sponsor submitted four-phase III studies, CR200.0126, CR200.0143, CR200.0124, and K.245.5005 (protocol number) to support the use of Creon® Minimicrospheres Capsules to treat adult and pediatric patients with exocrine pancreatic insufficiency. Of the four studies, the sponsor indicated that the three studies CR200.0126, CR200.0143, and CR200.0124 were

considered as pivotal studies while the other one K.245.5005 was supportive. However, for the study with protocol number K.245.5005, the sponsor further indicated that the overall conduct of the study and the verification of the source documentation for the essential data elements generated in the study were doubted by US and European Solvary Pharmaceuticals Compliance Audit. As a result, the remaining three main studies CR200.0126, CR200.0143, and CR200.0124 are the focus of this review.

Of the three studies, the two Studies CR200.0126 and CR200.0143 were for the treatment of steatorrhea in patients with cystic fibrosis while Study CR200.0124 was for the treatment of steatorrhea in patients with chronic pancreatitis. Furthermore, Study CR200.0126 recruited pediatric and adolescent patients with ages from 7 to 18 years while Studies CR200.0143 and CR200.0124 enrolled adults (ages ≥ 18).

Noted by this reviewer, the study designs for the two Studies CR200.0126 and CR200.0143 were alike, except for ages: Study CR200.0126 for patients with ages from 7 to 18 years while Study CR200.0143 for patients with ages ≥ 18. Due to similar study-design background, the background information for the two Studies CR200.126 and CR200.0143 is presented together. Then, presenting the background information for Study CR200.0124 is ensued.

<u>Studies CR200.0126 & CR200.0143</u>

The primary objective of the two studies was to compare the effectiveness of Creon®20 (20,000 USP lipase units) Minimicrospheres capsules to placebo in the treatment of steatorrhea in cystic fibrosis patients with exocrine pancreatic insufficiency who were maintained on a high fat diet. Both were randomized, double-blinded, parallel group, and multi-center studies.

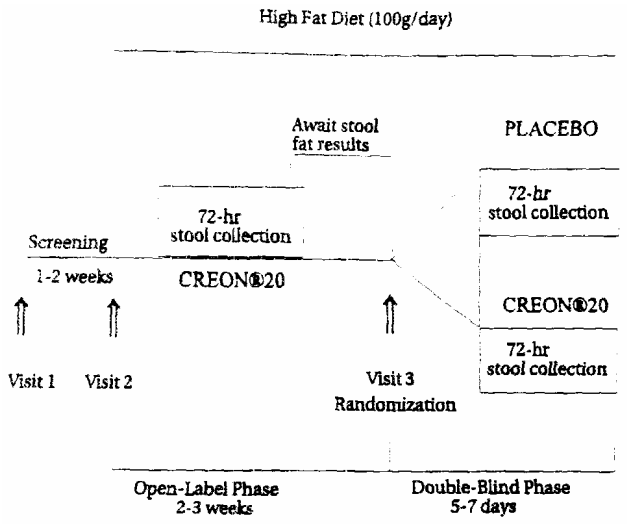
Following a one- to two-week screening period, patients who met the inclusion and not the exclusion criteria were entered into the open-label portion of the study where they began a controlled high fat diet. During the controlled high fat diet, individual patient adjusted the number of Creon®20 capsules taken per meal to maximize clinical effect. When an optimal dose was reached and maintained for at least two days, as evidenced by the minimization of clinical symptoms, and after at least three days on the high fat diet, patients entered the clinic to begin a 72-hour stool collection. While awaiting the results of the fecal fat analysis, patients were instructed to maintain the high fat diet and continue the Creon 20 dose taken at the time discharge. Based on the coefficient of fat absorption (CFA) calculated from the 72-hour stool collection, patients were either excluded from further participation in the study (≤ 80% CFA) or entered the double-blind portion of the study (> 80% CFA).

Qualified patients (with CFA > 80%) were randomized to receive either placebo or Creon®20 dose determined during the open label run-in phase. After a minimum two days of double-blind treatment, patients were admitted to the clinic for the 72-hour stool collection. It was anticipated that treatment time in the double-blind phase would range from 5 to 7 days depending upon gastrointestinal transit time determined by orally ingested stool markers (food dye).

From the screening time to the completion of the end-of-study assessments, patients and/or parents were asked to record diet information and enzyme supplement dose on a nutritional worksheet. Number of bowel movements and stool consistencies (hard, formed/normal, soft, or watery) were to be recorded on a daily stool diary during screening and while in the clinical unit. Clinical global improvement (CGI) was assessed at the end of the study using a 7-point physician-rated scale from "very much worse" to "very much improved".

The diagram for the study design is pictured by Figure 2.1.1.

Figure 2.1.1 Diagram for Study Design



For Study CR200.0126, forty-seven patients were enrolled in the Creon® 20 open-label treatment phase. Thirty-eight qualified CF patients (ages from 7 to17 years old) with clinical exocrine pancreatic insufficiency were randomized. Of these 38 patients, 20 and 18 were randomized to placebo and to Creon®, respectively. Then, thirty-six patients (18 placebo, 18 Creon® 20) completed the study. Similarly, for Study CR200.0143, fifty patients were enrolled in the Creon® 20 open-label treatment phase. Thirty-six qualified CF patients (ages from 18 to 54 years old) with clinical exocrine pancreatic insufficiency were randomized. Of the 36 patients, 18 patients were randomly assigned to each of the two treatment groups, placebo and Creon 20. Thirty-four patients (17 each) successfully completed the study. For both studies, the two patient populations were defined as follows:

1) Total patient population: consisted of all patients enrolled into the open-label phase of the study who took at least one dose of open-label study drug.
2) Intent-to-Treat (ITT) patient population: consisted of all patients randomized into the double-blind phase of the study who took at least one dose of double-blind study drug.

As indicated by the sponsor, Intent-to-Treat patient population was to be used in the efficacy analysis while the total patient population was for the safety analysis.

The primary efficacy endpoint was the change from baseline to final assessment in the coefficient of fat absorption (CFA). Baseline CFA was to be determined from the 72-hour stool collection at the end of the open-label phase. Final CFA was to be determined from the 72-hour stool collection at the end of the double-blind phase.

The secondary efficacy endpoints were bowel movement frequency, stool consistency, and clinical global improvement (CGI) and were to be summarized by treatment group. Bowel movement frequency and stool consistency from both the open-label and double-blind phases were to be examined.

A fixed-effect analysis of variance with treatment, center, and treatment by center interaction was to be performed to test the null hypothesis that mean change from baseline CFA in the CREON®20 group is equal to that in the placebo group. If appropriate, analysis of covariance using appropriate covariates was to be performed. Each of the statistical tests was to be two-sided and was to be considered statistically significant if $p \leq 0.05$.

With 40 patients (20 per treatment), Type I error rate of 0.05, and standard deviation of 21.54, this study was to have greater than 80% power to detect a difference of 20 points in change from baseline CFA between Creon®20 and placebo.

The dispositions of patients for Studies CR200.126 and CR200.0143 are presented in Table 2.1.1 and Table 2.1.2, respectively.

Table 2.1.1 (Sponsor's) Patient disposition by treatment and center for Study CR200.0126

Center Number	Investigator	Patients not Randomized to *Double-Blind*		Patients Randomized to *Double Blind*				Total	
				Placebo		CREON®20			
		N	%	N	%	N	%	N	%
01	(b) (4)	3	33.3	5	25.0	4	22.2	12	25.5
02		1	11.1	4	20.0	3	16.7	8	17.0
03		0	0.0	5	25.0	5	27.8	10	21.3
04		0	0.0	2	10.0	2	11.1	4	8.5
05		4	44.4	1	5.0	2	11.1	7	14.9
06		1	11.1	3	15.0	2	11.1	6	12.8
Totals		9	100.0	20	100.0	18	100.0	47	100.0

Table 2.1.2 (Sponsor's) Patient disposition by treatment and center for Study CR200.0143

Center Number	Investigator	Patients not Randomized to Double-Blind		Patients Randomized to Double Blind				Total	
				Placebo		CREON®20			
		N	%	N	%	N	%	N	%
01	(b) (4)	5	35.7	3	16.7	2	11.1	10	20.0
02		1	7.1	4	22.2	4	22.2	9	18.0
03		1	7.1	2	11.1	2	11.1	5	10.0
04		4	28.6	6	33.3	6	33.3	16	32.0
05		2	14.3	0	0.0	1	5.6	3	6.0
06		1	7.1	3	16.7	3	16.7	7	14.0
Totals		14	100.0	18	100.0	18	100.0	50	100.0

For Study CR200.0126, Table 2.1.1 indicated that forty-seven cystic fibrosis patients were entered into the study from six investigative centers. Centers 1 and 3 enrolled the greatest numbers of patients totaling close to half (46.8%) the number of patients entering the study. Of the 47 patients who entered the open-label phase, nine were not randomized to double-blind treatment.

Of the 47 patients screened and entered into open-label treatment, 38 qualified patients were randomized into double-blind phase with 20 patients receiving placebo and 18 patients receiving Creon®20. Thirty-six of the 38 randomized patients completed the study: 18 in each group.

For Study CR200.0143, Table 2.1.2 indicated that fifty cystic fibrosis patients entered into the study from six investigative centers. Centers 1 and 4 had the highest enrollments, totaling more than half the number of patients entering the study. Of the 50 patients who entered the open-label phase, 14 were not randomized to double-blind treatment. Of the 50 patients entered into open-label phase, 36 qualified patients entered the double-blind phase and were randomized into the two treatment groups (placebo and Creon®20) with 18 patients each. Then, thirty-four of the 36 randomized patients completed the study: 17 in each group.

<u>Studies CR200. 0124</u>

The primary objective was to demonstrate the effect of Creon®10 (10000 lipase USP units) on fat absorption in patients with exocrine pancreatic insufficiency caused by chronic pancreatitis.

This study was a multi-center, randomized, double-blinded, placebo-controlled, parallel group trial comparing the safety and efficacy of Creon® 10 versus placebo for the treatment of steatorrhea in patients with chronic pancreatitis. Patients with documented chronic pancreatitis and a history of steatorrhea requiring pancreatic enzyme supplementation were to be recruited from approximate 30 centers. Allowing for a 20% rate of post-enrollment non-evaluability and attrition, a total of 68 eligible patients were to be enrolled in the study to ensure that 54 patients would complete the double-blind treatment phase. The study design is summarized in Figure 2.1.3.

Figure 2.1.3 Diagram for Study Design

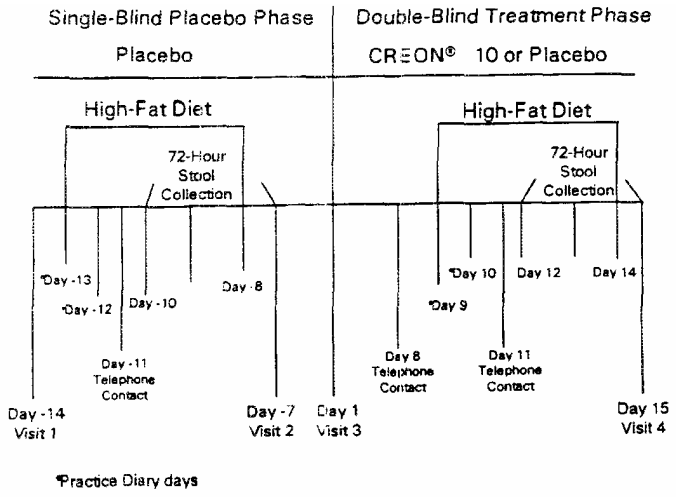


Figure 2.1.3 indicated that the study period consisted of two-part treatment phases: a two-week single-blinded placebo run-in phase followed by two weeks of double-blind treatment phase. Furthermore, stools were collected for determination of fat content during the final 72-hours of each treatment period. Average daily fat excretion was calculated for each collection period. During these periods, patients were also required to record on diary cards the number of stools and describe the consistency of each stool. By checking a box on the diary cards, patients rated stool consistency as hard (coded as 0), formed/normal (coded as 1), soft (coded as 2), or watery (coded as 3). In addition, at each scheduled visit, both the patient and the investigator independently evaluated the patient's general disease status, including pain, using the clinical global improvement of disease symptom (CGIDS) assessed with a 5-point rated scale from none (symptoms not presented) to incapacitating (symptoms prevent patients from normal activity).

Patients who met the inclusion and not the exclusion criteria were proceeded into a two-week single-blinded placebo run-in phase of the study. Patients who had a stool fat excretion ≥ 10 g/day and a CFA < 80% during the single-blind placebo phase were randomly assigned (1:1 distribution) at visit 3 (Day 1) to receive two weeks of treatment with either Creon® 10 or placebo. Patients who did not meet these criteria were discontinued from further treatment. During both treatment phases, study medications were administered orally in divided daily doses of four capsules with each meal and two capsules with snacks. The minimum and maximum dosages allowed by protocol were 10 and 24 capsules per day, respectively.

Patients were provided with diet consultation, which included instruction to consume at least 100 g of fat daily on Days -13 to -8 and 9 to 14 (high-fat days). To assist in the selection of foods, each patient was provided with a list of high-fat foods, which identified the fat content of each item. Patients were required to maintain a nutrition diary, in which the daily diet (all foods and beverages) was recorded on these high-fat days.

The efficacy analysis was to be performed on the Intent-to-Treat (ITT) population: patients randomized into the double-blind phase of the study and taking at least one capsule of assigned study medication. However, the safety analysis was to be performed on patients who received at least one dose of double-blind study medication (Creon® 10 or Placebo) and had data for at least one safety parameter.

The primary efficacy parameter was to be the change in CFA from baseline (Day 1 of the double-blind phase before any double-blind medication was taken by the patient) to the Day 15 assessment. An analysis of variance (ANOVA) with treatment as a fixed factor was to be performed to test the null hypothesis that mean change from baseline CFA at the final assessment in the Creon®10 group was equal to that in the placebo group. If appropriate, analysis of covariance using appropriate covariates was to be performed. Each of the statistical tests was to be two-sided and was to be considered statistically significant if $p \leq 0.05$.

The secondary efficacy endpoints were stool frequency, stool consistency, and stool fat. These data were to be summarized by treatment group comparing change from baseline measurements. The CGIDS assessments completed by the investigator and the patient were also to be summarized by treatment group.

With 54 patients (27 per treatment group), Type I error rate of 0.05, and standard deviation of 18.23 (estimated from previous study), this study was to have greater than 80% power to detect a difference of 15 in change from baseline CFA between Creon®10 and placebo.

A total of 64 patients were enrolled in the single-blind placebo phase of the study. Of the 64 enrolled patients, the sponsor indicated that 27 qualified patients (42.2%) entered the double-blind phase and completed the study. Patients who entered the double-blind phase were evenly distributed across 16 centers. Among these 27 patients, 13 were randomized to treatment Creon® 10 and 14 received placebo. Patient enrollment into the double-blind phase by investigator (Center #) is summarized in Table 2.1.3.

Table 2.1.3 (Sponsor's) Patient disposition by treatment and center for Study CR200.0124

Investigator (Center #)	Placebo (N =14)	CREON® 10 (N = 13)
(b) (4)	1 (7.1%)	1 (7.7%)
	1 (7.1%)	1 (7.7%)
	1 (7.1%)	0 (0.0%)
	1 (7.1%)	0 (0.0%)
	2 (14.3%)	0 (0.0%)
	2 (14.3%)	0 (0.0%)
	0 (0.0%)	1 (7.7%)
	1 (7.1%)	2 (15.4%)
	0 (0.0%)	1 (7.7%)
	1 (7.1%)	0 (0.0%)
	1 (7.1%)	0 (0.0%)
	1 (7.1%)	0 (0.0%)
	0 (0.0%)	2 (15.4%)
	0 (0.0%)	1 (7.7%)
	1 (7.1%)	3 (23.1%)
	1 (7.1%)	1 (7.7%)

2.2 Statistical Evaluation of Evidence on Efficacy/Safety

2.2.1 Detail Review for Individual Studies

2.2.1.1 Study CR200.0126

Demographic Data and Baseline Charasteristics

Table 2.2.1.1.1 presented patient demographic characteristics for race and sex using ITT patient population.

Table 2.2.1.1.1 (Sponsor's) Patient demographic characteristics using ITT population

Patient Characteristics		Placebo		CREON®20		Total		p-value
		N=20		N=18		N=38		
		N	%	N	%	N	%	
RACE	Caucasian	20	100.0	16	88.9	36	94.7	0.325
	Negroid			1	5.6	1	2.6	
	Other			1	5.6	1	2.6	
SEX	Male	11	55.0	7	38.9	18	47.4	0.181
	Female	9	45.0	11	61.1	20	52.6	

p-values based on Cochran-Mantel-Haenszel general association statistic, controlling for center.

Table 2.2.1.1.1 indicated that of the thirty-eight ITT patients, eighteen patients were males and twenty were females. For race, of the thirty-eight patients, thirty-six were Caucasian (twenty in the placebo group and sixteen in the Creon®20 group), one was African-American (Creon®20)

and one was mixed-race (Creon®20). The results showed that there were no significant differences between treatment groups for sex and race.

The sponsor also reported that the mean age in the placebo group was 12.8 years while for Creon®20, the mean age was 12.1 years. The mean height and weight for the placebo group were 148 cm and 39 kg, respectively while for the Creon®20 group, the mean height and weight were 146 cm and 37 kg, respectively. Similarly, there were no significant differences between treatment groups for age, height, and weight.

As for the baseline characteristics, the sponsor emphasized that as evidenced by the medical history data collected at screening, the ITT patient appeared to be representative of the general pediatric and adolescent population diagnosed with cystic fibrosis with no apparent differences between the two treatment groups. In addition, conditions of the special senses and musculoskeletal body systems were also frequently noted in both p!acebo (45%) and Creon®20 (33%) treatment groups, as were non-drug related allergies (placebo: 40*%;* Creon®20: 44%).

Efficacy analysis Results and Conclusions

The coefficient of fat absorption (CFA) is based on the fat ingested (g/24 hrs) and the fat excreted (g/24 hrs) during the 72-hour stool collections. Nineteen placebo and eighteen Creon®20 patients who completed stool collections in both treatment phases were included in the analysis. One placebo patient (60207) withdrew from the study due to an adverse event before the double-blind stool collection was started and was not included in the analysts. Table 2.2.1.1.2 presented the changes in CFA from open-label phase to double-blind treatment phase by treatment group.

Table 2.2.1.1.2 (Sponsor's) CFA changes from open-label to double-blind treatment phases (ITT population)

Open-label phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 20		Placebo		Creon 20		Placebo		Creon 20	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
87	19	87	18	52	19	84	18	-35	19	-3.0	18
								p-value# < 0.001*			

#: p-value calculated based on analysis of variance model with factors for center, treatment, and center by treatment interaction.
*: Significant at .05 significance level.

Table 2.2.1.1.2 indicated that the mean CFAs of the placebo (87%) and Creon®20 (87%) treatment groups were comparable following open-label phase in which patients were treated with Creon®20. However, following double-blind treatment phase, the CFA means for the two groups were different: 52% for the placebo group versus 84% for the Creon®20 group. The change in the mean CFA from the open-label phase to the double-blind treatment phase was significant ($p < 0.001$) between the two treatment groups using analysis of variance method with center, treatment, and center by treatment as model parameters. In addition, the sponsor emphasized that the analysis of covariance method using baseline CFA as a covariate showed result similar to Table 2.2.1.2.

For the secondary endpoint analysis on stool frequency, Table 2.2.1.1.3 presented the mean stool

frequency for open-label and double-blind stool collection periods and the mean change in stool frequency from open-label to double-blind stool collection period by treatment group using ITT patient population.

Table 2.2.1.1.3 (Sponsor's) Stool frequency by treatment group using ITT population

Open-label (OL) Stool Collection Period				Double-blind treatment (DB) Stool Collection Period				Change from OL to DB			
Placebo		Creon 20		Placebo		Creon 20		Placebo		Creon 20	
N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
19	8.1	18	9.2	19	12.4	18	8.1	19	4.3	18	-1.1
								p-value# = 0.002*			

#: p-value calculated based on analysis of variance model with factors for center, treatment, and center by treatment interaction.
*: Significant at .05 significance level.

From Table 2.2.1.1.3, the sponsor indicated that the number of stools during the open-label stool collection was comparable between the two treatment groups. However, the change in mean stool frequency from open-label to double-blind was significantly different between treatments (p=0.002). An increase in stool frequency occurred from open-label to double blind phase in the placebo treatment group (8.1 to 12.4). On the contrary, the mean stool frequency decreased from open-label to double blind phase in the Creon®20 treatment group (9.2 to 8.1).

Similarly, the sponsor reported that for the other two secondary endpoints stool consistency and clinical global improvement (CGI), the analysis results showed that patients in the Creon group were significantly better than those in the placebo group (p=0.001 for stool consistency and p<0.001 for CGI).

Results of Adverse Events

An adverse event was defined as treatment emergent during the open-label or double-blind treatment phase if the start date of the event was equal to or greater than the start date of the treatment phase. The most frequent treatment emergent adverse events reported by patients were in the three body systems: body as a whole, respiratory and digestive.

The sponsor further indicated that an increase in abdominal pain following double-blind placebo treatment was the largest treatment difference, 55% (11/20) for placebo and 11% (2/18) for Creon 20. There were no differences between the two treatment groups in the frequency of other treatment emergent adverse events, and the types of events reported during this study were not unexpected for patients with cystic fibrosis. In addition, a comparison of change-from-screening physical exams and reports of markedly abnormal laboratory or vital signs showed no apparent treatment differences.

Finally, the sponsor concluded that Creon 20 capsules are safe at the doses used in this study to control the symptoms of fat malabsorption in children and adolescents with cystic fibrosis.

2.2.1.2 Study CR200.0143

Demographic Data and Baseline Charasteristics

Table 2.2.1.2.1 presented patient demographic characteristics for race and sex using ITT patient population.

Table 2.2.1.2.1 (Sponsor's) Patient demographic characteristics using ITT population

Patient Characteristics		Placebo N=18		CREON® N=18		Total N=36		p-value*
		N	%	N	%	N	%	
RACE	CAUCASIAN	18	100.0	18	100.0	36	100.0	.
SEX	MALE	12	66.7	10	55.6	22	61.1	0.587
	FEMALE	6	33.3	8	44.4	14	38.9	.

* p-value based on Cochran-Mantel-Haenszel general association statistic, controlling for center, using center pooling.

Table 2.2.1.2.1 indicated that of the thirty-six ITT patients, twenty-two patients were males and fourteen were females. All thirty-six patients were Caucasian. The results showed that there were no significant differences between treatment groups for sex.

The sponsor also reported that the mean age in the placebo group was 24.4 years while for Creon®20, the mean age was 23.3 years. The mean height and weight for the placebo group were 165.2 cm and 54.3 kg, respectively while for the Creon®20 group, the mean height and weight were 166.6 cm and 54.1 kg, respectively. Similarly, there were no significant differences between treatment groups for age, height, and weight.
For the baseline characteristics, the sponsor emphasized that as evidenced by the medical history data collected at screening, the ITT patient appeared to be representative of the general CF population with exocrine pancreatic insufficiency and mild to moderate lung disease. Greater than 50% of placebo and Creon®20 patients reported conditions associated with the special senses (placebo 72.2%: Creon®20 55.6%), metabolic and nutritional (placebo 94.4%; Creon®20 94.4%), and musculoskeletal (placebo 77.8%; Creon®20 61%) body systems. In addition, placebo patients reported more drug (72.2%) and non-drug (50.0%) allergies than Creon®20 patients (33.3% and 33.3%, respectively). Finally, the sponsor concluded that the two treatment groups were considered essentially the same with respect to medical history despite the differences between treatment groups for drug and non-drug allergy histories.

Efficacy analysis Results and Conclusions

The coefficient of fat absorption (CFA) is based on the fat ingested (g/24 hrs) and the fat excreted (g/24 hrs) during the 72-hour stool collections. Eighteen placebo and eighteen Creon®20 patients completed stool collections in both treatment phases and are included in the analysis. The sponsor indicated that in order to provide inferential statistics, it was necessary to pool the data from center 5 (one patient) with the next center, Center 6 (6 patients).

Table 2.2.1.2.2 presented the changes in CFA from open-label phase to double-blind treatment phase by treatment group.

Table 2.2.1.2.2 (Sponsor's) CFA changes from open-label to double-blind treatment phases (ITT population)

Open-label phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 20		Placebo		Creon 20		Placebo		Creon 20	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
88	18	89	18	51	18	87	18	-37	18	-2	18
								$P^{\#}$=0.000*			

#: p-value calculated based on analysis of variance model with factors for center, treatment, and center by treatment interaction.
*: Significant at .05 significance level.

Table 2.2.1.2.2 indicated that the mean CFAs of the placebo (88%) and Creon®20 (89%) treatment groups were comparable following the open-label phase in which patients were treated with Creon®20. Furthermore, following the double-blind treatment phase, the change in the mean CFA from open-label to double-blind treatment was significant ($p< 0.001$) between Creon®20 (-2%) and placebo (-37%) using analysis of variance method with center, treatment, and center by treatment as model parameters. However, the sponsor also declared that the analysis of variance test also showed that the interaction between treatment and center was significant ($p=0.07$). [The sponsor did not specify a significance level for treatment-by-center interaction test in the protocol.] To deal with this issue, the sponsor further indicated that the fecal fat excreted by patient 60254 following double-blind placebo treatment exceeded the amount of dietary fat ingested. After excluding this patient from the CFA analysis, the interaction of treatment by center was not shown significant ($p=0.26$) and the CFA changes from the open-label phase to the double-blind treatment phase between the two treatment groups were still significant ($p<0.001$). Thus, the sponsor concluded that the inclusion or exclusion of patient 60254 from the analysis did not alter the level of significance seen in the treatment comparisons with regard to the mean change of CFA from the open-label phase to the double blind phase. However, the significant interaction between treatment and center is further assessed in the section of Reviewer's analysis and comments.

Finally, the sponsor emphasized that the analysis of covariance method using baseline CFA as a covariate showed result similar to Table 2.2.1.2.

For the secondary endpoint analysis of stool frequency, Table 2.2.1.2.3 presented the mean stool frequency for the open-label and double-blind stool collection periods and the mean change in stool frequency from the open-label to double-blind stool collection periods by treatment group using ITT patient population.

Table 2.2.1.2.3 (Sponsor's) Stool frequency by treatment group using ITT population

Open-label (OL) Stool Collection Period				Double-blind treatment (DB) Stool Collection Period				Change from OL to DB			
Placebo		Creon 20		Placebo		Creon 20		Placebo		Creon 20	
N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
18	7.6	18	7.2	18	14.1	18	6.6	18	6.5	18	-0.6
								$P^{\#}$=0.000*			

#: p-value calculated based on analysis of variance model with factors for center, treatment, and center by treatment interaction.
*: Significant at .05 significance level.

From Table 2.2.1.2.3, the sponsor indicated that the number of stools during the open-label stool collection was comparable between the two treatment groups. However, the change in mean stool frequency from open-label to double-blind was significantly different between treatments ($p<0.001$). An increase in stool frequency occurred from open-label to double-blind phase (7.6 to 14.1) in the placebo treatment group. On the contrary, the mean stool frequency decreased from open-label to double-blind phase in patients receiving Creon®20 treatment (7.2 to 6.6).

Similarly, the sponsor reported that for the other two secondary endpoints stool consistency and clinical global improvement (CGI), the analysis results showed that patients in the Creon group were significantly better than those in the placebo group ($p=0.001$ for stool consistency and $p<0.001$ for CGI).

Results of Adverse Events

The sponsor indicated that an increase in abdominal pain following double-blind placebo treatment was the largest treatment emergent difference seen in the treatment adverse events. Nine of eighteen (50.0%) patients who received placebo during double-blind treatment phase reported abdominal pain compared to two of eighteen (11 %) patients who received Creon®20 capsules during this phase.

Antiflatulent use increased in placebo patients during double-blind treatment phase compared to one (5.6%) patient in the Creon®20 group. In addition, a comparison of change from screening to termination, physical exam showed three (16.7%) placebo patients with abdominal tenderness or distension at termination compared to no Creon®20 patients with these findings.

There were no differences between the two treatment groups in the frequency of other treatment emergent adverse events, and the types of events reported during this study were not unexpected for patients with cystic fibrosis. In addition, reports of markedly abnormal laboratory, or vital signs showed no apparent treatment differences.

To determine if clinically effective (CFA>80%) doses of Creon®20 produced significant changes in serum or urinary uric acid concentrations, a treatment comparison of the change from open-label to double-blind treatment was undertaken. No hyperuricemia was seen in either treatment group. There was a greater decrease in mean urinary uric acid concentrations from open-label to double-blind in patients randomized to placebo compared to Creon®20 treatment. However, this difference was not statistically significant.

Finally, the sponsor concluded that Creon 20 capsules are safe at the doses used in this study to control the symptoms of fat malabsorption in adults with cystic fibrosis.

2.2.1.3 Study CR200.0124

Demographic Information

Table 2.2.1.3.1 presented patient demographic characteristics for race and sex using ITT patient population.

Table 2.2.1.3.1 (Sponsor's) Patient demographic characteristics using ITT population

	Placebo	CREON® 10	p-Value*
Age (years)			
N	14	13	-
Mean (s.e.)	51.0 (3.0)	51.9 (2.7)	0.8213
Min - Max	31 - 69	38 - 74	-
Sex			
Female	6 (42.9%)	3 (23.1%)	0.4197
Male	8 (57.1%)	10 (76.9%)	-
Race			
Caucasian	9 (64.3%)	7 (53.8%)	0.8383
Negroid	5 (35.7%)	5 (38.5%)	-
Oriental	0 (0.0%)	0 (0.0%)	-
Filipino	0 (0.0%)	1 (7.7%)	-

* ANOVA for H_0: Treatment means are equal for age; or Fisher's Exact Test for H_0: No association between variable and treatment group for Sex and Race.

Table 2.2.1.3.1 indicated that of the twenty-seven ITT patients, eighteen patients were males and nine were females. For race, sixteen of the twnty-seven patients were Caucasian (nine in the placebo group and seven in the Creon®10 group), ten were Negroid, and one was Filipino (Creon®10). The results showed that there were no significant differences between treatment groups for sex and race.

The sponsor also reported that the mean age in the placebo group was 51 years while for Creon®10, the mean age was 52 years. Similarly, there was no significant difference between treatment groups for age.

Efficacy analysis Results and Conclusions

Table 2.2.1.3.2 presented the changes in CFA from single-blind placebo phase to double-blind treatment phase by treatment group. Noted by this reviewer, one patient in the Creon®10 group without CFA data for the double blind treatment phase was excluded from the analysis.

Table 2.2.1.3.2 (Sponsor's) CFA changes from open-label to double-blind treatment phases (ITT population)

Single-blind Placebo phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 10		Placebo		Creon 10		Placebo		Creon 10	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
56	14	50	12	68	14	87	12	12	14	37	12
								$P^{\#}$ =0.019*			

#: p-value calculated based on analysis of variance method with treatment as parameter.
*: Significant at .05 significance level.

Table 2.2.1.3.2 indicated that the change in mean CFA from the single-blind placebo to the double-blind phases between treatments was significantly different (p = 0.019). Furthermore, additional analysis of CFA was performed excluding patient 60109 whose fat excretion was greater than fat intake during the single-blind placebo phase. The result showed that the changes in the mean CFA from the single-blind placebo to the double-blind phases between treatments remained significantly different (p=0.023).

In addition, the sponsor also performed the treatment efficacy comparison on the change in mean CFA from the single-blind placebo to the double-blind phases (the primary endpoint point) using ANCOVA model with treatment and baseline (single-blind placebo phase) CFA as model variables/parameters. However, the sponsor did not pre-specify in the protocol that the baseline CFA was to be used as a covariate in the ANCOVA analysis. Especially, the primary/first-choice efficacy analysis specified by the sponsor in the protocol was the ANOVA method with the treatment effect as the only model parameter. As a consequence, the ANCOVA analysis using baseline CFA as covariate is deemed as a post-hoc analysis and is not further considered in the sensitivity analysis demonstrated in Sub-section 2.2.2.3.1 "Reviewer's Statistical Analysis".

For the secondary endpoint analysis of stool frequency, Table 2.2.1.3.3 presented the mean stool frequency for the open-label and double-blind stool collection periods and the mean change in stool frequency from the open-label to double-blind stool collection periods by treatment group using ITT patient population.

Table 2.2.1.3.3 (Sponsor's) Stool frequency by treatment group using ITT population

Open-label (OL) Stool Collection Period				Double-blind treatment (DB) Stool Collection Period				Change from OL to DB			
Placebo		Creon 10		Placebo		Creon 10		Placebo		Creon 10	
N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
14	14.0	13	10.8	14	14.6	13	5.2	14	0.6	13	-5.6
								$P^{\#}$ = 0.0015*			

#: p-value calculated based on analysis of variance model with treatment as parameter.
*: Significant at .05 significance level.

From Table 2.2.1.3.3, the sponsor indicated that in the Creon® 10 group, mean stool frequency during the single-blind placebo phase and the double-blind phase was 10.8 and 5.2 stools, respectively, versus 14.0 and 14.6 stools, respectively for the single-blind placebo phase and the double-blind phase in the Placebo group. The mean change in daily stool frequency from the single-blind placebo to the double-blind phases was significantly different (p = 0.0015) between Creon® 10 and placebo.

Similarly, the sponsor reported that for the other two secondary endpoints fat excretion, stool consistency, the analysis results showed that patients in the Creon group were significantly better than those in the placebo group (p=0.018 for fat excretion and p=0.01 for stool consistency). However, no significant differences between the two treatment groups were detected for clinical global impression of disease symptoms (CGIDS) assessed by both investigator scores (p=0.10) and patient scores (p=0.13), using Fisher's Exact tests.

Results of Adverse Events

The sponsor indicated that there was no significant difference existed between groups in either the number of patients reporting at least one treatment-emergent adverse event (p = 0.68 by Fisher's Exact test) or in the number of patients with possibly drug-related treatment-emergent adverse events (p = 0.48 by Fisher's Exact test).

In the Creon® 10 group, six treatment-emergent adverse events occurred in three of the 13 patients. Of the treatment-emergent events, two were considered possibly drug-related by the Invesigator. These events were asthenia and tremor occurred with Patient # 60095. No medical treatment or intervention was required. As for the 14 patients in the Placebo group, five patients experienced 11 treatment-emergent adverse events. None of these events was considered related to the study medication. In addition, no serious adverse events were reported during the double-blind phase on the study.

Finally, the sponsor concluded that Creon® 10 at dosages of 10 to 24 capsules per day, is well tolerated.

2.2.2. Statistical Reviewer's Findings

2.2.2.1 Study CR200.0126

2.2.2.1.1 Reviewer's Statistical Analysis

In order to validate the sponsor's efficacy claim, this reviewer performs the following three analyses: 1.) ANCOVA analysis, 2.) Change-in-CFA analysis by center, 3.) Subgroup analyses. Data sets used by this reviewer's analysis were submitted by the sponsor on June 27, 2003.

1) ANCOVA analysis

In this analysis, the CFA value at the end of double blind phase is the dependent variable of the ANCOVA model with treatment effect, center, treatment by center, and baseline CFA as the explanatory variables (model parameters). The logic for performing this analysis is to assess if the superiority of Creon to placebo sensitive to the different analysis model. Table 2.2.2.1.1 presents the results.

Table 2.2.2.1.1 (Reviewer's) ANCOVA analysis with baseline CFA to compare treatment effects using ITT patients

Placebo (P)		Creon 20 (C)		
MCFAD[1]	(N)	MCFAD	(N)	P-value for comparing P and C
52%	(19)	84%	(18)	0.0001*

1: mean of CFA at end of double blind phase; *: significant at .05 significance level;
Note: p-value calculated from ANCOVA model with treatment, center, treatment by center, and baseline CFA as parameters.

Table 2.2.2.1.1 indicates that the mean CFA for Creon®20 at the end of double-blind phase is significant (p= 0.0001) higher than that of placebo using analysis of covariance model with treatment, center, center by treatment, and baseline CFA as model parameters.

2) Change-in-CFA analysis by center

In order to investigate if the efficacy of Creon®20 superior to that of placebo dominated by aberrant centers, this reviewer computes the mean change in CFA from the open-label phase to the double-blind phase (the primary endpoint) by center using ITT patient population. Table 2.2.2.1.2 presents the results.

Table 2.2.2.1.2 (Reviewer's) Mean change in CFA (%) from open-label phase to double-blind phase by center (ITT)

	Center 1		Center 2		Center 3		Center 4		Center 5		Center 6	
Treatment Group	MDCFA[1]	N	MDCFA	N	MDCFA	N	MDCFA	N	MDCFA	N	MDCFA	N
Placebo	-48.9	5	-37.8	4	-33.6	5	-13.3	1	-43.7	1	-14.2	3
Creon®20	-8.7	4	2.8	3	-5.2	5	2.4	2	-4.2	2	-1.4	2

1: Mean change in CFA from open-label phase to double-blind phase.

Table 2.2.2.1.2 shows that the variation of mean changes in CFA by center for patients in the placebo group is much larger than that of patients in the Creon®20 group. In addition, the mean change in CFA (–48.9) for placebo in center 1 is the lowest value among the six centers.

In order to assess the impact of the patients in center 1 on the superiority of Creon®20 to placebo, this reviewer performs the sponsor's analysis method for the mean change in CFA from the open-label phase to the double-blind phase using ITT patients excluding from center 1. Table 2.2.2.1.3 presents the result.

Table 2.2.2.1.3 (Reviewer's) CFA changes from open-label to double-blind treatment phases (ITT patients excluding center 1)

Open-label phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 20		Placebo		Creon 20		Placebo		Creon 20	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
88	14	87	14	58	14	85	14	-30	14	-2.0	14
								p-value[#] = 0.002*			

[#]: p-value calculated based on analysis of variance model with factors for center, treatment, and center by treatment interaction.
*: Significant at .05 significance level.

Table 2.2.2.1.3 shows that after excluding patients from center 1, the change in the mean CFA from the open-label phase to the double-blind treatment phase is still significant (p = 0.002) between the two treatment groups using analysis of variance method with center, treatment, and center by treatment as model parameters.

3) Subgroup analyses.

In order to assess the consistency of the treatment effect of Creon®20 over placebo across subgroups, this reviewer performed the subgroup analysis using the sponsor's general linear model on the primary endpoint (change in CFA) based upon ITT patient population. The subgroups analyzed are Gender (Male and Female), Race (Caucasian and non-Caucasian), and Age group (age # 12 and age > 12). Since this study enrolled the pediatric and adolescent patients, in the age subgroup analysis, patients are divided into patients with ages not greater than 12 (age # 12) and patients with ages greater than 12 (age > 12).

Gender

Table 2.2.2.1.4 presents the results of treatment efficacy comparisons for Creon®20 versus placebo by gender.

Table 2.2.2.1.4 (Sponsor's) CFA changes from open-label to double-blind treatment phases (ITT population)
Male

Open-label phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 20		Placebo		Creon 20		Placebo		Creon 20	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
86	11	87	7	41	11	80	7	-45	11	-7.0	7
										$P^{\#}$ = 0.004*	

Female

Open-label phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 20		Placebo		Creon 20		Placebo		Creon 20	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
87	9	88	11	68	9	87	11	-19	9	-1.0	9
										$P^{\#}$ = 0.007*	

#: p-value calculated based on analysis of variance model with factors of center, treatment, and center by treatment interaction.
*: Significant at .05 significance level.

Table 2.2.2.1.4 indicates that at significance level of 0.05, the efficacy of Creon®20 is superior to that of placebo assessed by the change in CFA from open-label phase to double-blind treatment phase for both females and males.

Race (Caucasian and non-Caucasian)

Since more than 90% of patients entered the double-blind treatment phase were Caucasian (White), no race analysis is performed.

Age group (age # 12 and age > 12)

Table 2.2.2.1.5 presents the results of treatment efficacy comparisons for Creon®20 versus placebo by age group.

Table 2.2.2.1.5 (Sponsor's) CFA changes from open-label to double-blind treatment phases (ITT population)
age # 12

Open-label phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 20		Placebo		Creon 20		Placebo		Creon 20	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
86	6	88	9	50	6	81	9	-36	6	-7.0	9
										$P^{\#}$ = 0.004*	

age > 12

Open-label phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 20		Placebo		Creon 20		Placebo		Creon 20	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
87	14	87	9	53	14	87	9	-34	14	-0.0	9
										$P^{\#}$ = 0.01*	

#: p-value calculated based on analysis of variance model with factors for center, treatment, and center by treatment interaction.
*: Significant at .05 significance level.

Table 2.2.2.1.5 indicates that at significance level of 0.05, the efficacy of Creon®20 is superior to that of placebo assessed by the change in CFA from open-label phase to double-blind treatment phase for both age groups.

2.2.2.1.2 Finding Remarks

- The ANCOVA analysis using CFA at the end of double blind phase as the dependent variable along with the treatment effect, center, treatment by center, and baseline CFA as the explanatory variables, performed by this reviewer, shows that Creon®20 is superior to placebo. It indicates that the superiority of Creon®20 to placebo is not sensitive to the different analysis model.
- Although the mean change in CFA for placebo in center 1 is much smaller than that of other centers, the superiority of Creon®20 to placebo still holds using patients excluding center 1. As a result, the superiority of Creon®20 to placebo is not dominated by centers with unusual data.

2.2.2.2 Study CR200.0143

2.2.2.2.1 Reviewer's Statistical Analysis

In order to validate the sponsor's efficacy claim, this reviewer performs the following three analyses: 1.) Impact assessment of the treatment by center interaction, 2.) ANCOVA analysis, and 3.) Subgroup analyses. Data sets used by this reviewer's analysis were submitted by the sponsor on June 27, 2003.

1) Impact assessment of the treatment by center interaction

In order to assess the impact of the significant interaction (p=0.07) between treatment and center on the treatment efficacy comparison, this reviewer performs the following two analyses using ITT patient population including patient 60254: i) Change-in-CFA analysis by center, and ii) Weighted analysis.

i.) Change in CFA analysis by center

Table 2.2.2.2.1 presents the mean changes in CFA from the open label phase to the double blind phase by treatment and center, using ITT patients including patient 60254 who had abnormal CFA in the double blind phase.

Table 2.2.2.2.1 (Reviewer's) Mean change in CFA (%) from open-label to double-blind phase by treatment and center

	Center 1		Center 2		Center 3		Center 4		Center 6[2]	
Treatment Group	MDCFA[1]	N	MDCFA	N	MDCFA	N	MDCFA	N	MDCFA	N
Placebo	-19.7	3	-21.4	4	-56.7	2	-32.2	6	-71.0	3
Creon®20	-2.4	2	0.73	4	-4.4	2	-2.0	6	-3.4	4

1: Mean change in CFA from open-label phase to double-blind phase; 2: one patient in center 5 assigned to center 6.

Table 2.2.2.2.1 indicates that the effect of Creon®20 is consistently better than that of placebo across the five centers. Thus, the significant interaction between treatment and center is deemed as a quantitative interaction. Since the treatment differences are in the same directions across the five centers, this reviewer performs the unweighted and weighted methods to assess the overall treatment effect of Creon®20 versus that of placebo across the five centers. The overall effect of each treatment calculated by the unweighted analysis is based on the simple average over the treatment effects of five individual centers while the weighted analysis uses weight inversely proportional to the variance of the estimated treatment effect for each center. As shown by Gallo in his paper titled "Center-weighting issues in multi-center clinical trials" published by Journal of Biopharmaceutical statistics, 10(2), 145-163 (2000), the unweighted method is equivalent to Type III sum of squares in SAS Proc GLM and weighted method is equivalent to SAS Type II sum of squares. The unweighted analysis was already done by the sponsor using SAS Type III sum of squares for a model with treatment, center, and treatment by center as parameters. The result was presented in Table 2.2.1.2.2. The p-value less than 0.001 indicated that the efficacy of Creon®20 (-2%) measured by the change in the mean CFA from the open-label phase to the double-blind treatment phase was superior to that (-37%) of placebo.

ii.) Weighted analysis

In order to explore the strength on the superiority of Creon®20 to placebo, this reviewer performs the weighted analysis on the change in CFA from the open-label phase to the double-blind treatment phase using SAS Type II sum of squares analysis with the same model the sponsor used for Type III analysis. The result is presented in Table 2.2.2.2.2.

Table 2.2.2.2.2 (Sponsor's) CFA changes from open-label to double-blind treatment phases

Open-label phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 20		Placebo		Creon 20		Placebo		Creon 20	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
88	18	89	18	51	18	87	18	-37	18	-2	18
								$P^{\#} < 0.0001$*			

#: p-value calculated based on analysis of variance model with factors for center, treatment, and center by treatment interaction.
*: Significant at .05 significance level.

Table 2.2.2.2.2 shows the change in the mean CFA from open-label to double-blind treatment phase, using weighted analysis method (Type II sum of squares), for Creon®20 (-2%) is still significantly ($p < 0.0001$) better that that (-37%) of placebo.

2) ANCOVA analysis

In this analysis, the CFA value at the end of double blind phase is the dependent variable of the ANCOVA model with treatment effect, center, treatment by center, and baseline CFA as the explanatory variables (model parameters). The logic for performing this analysis is to assess if the superiority of Creon®20 to placebo sensitive to different analysis model. Table 2.2.2.2.3 presents the results.

Table 2.2.2.2.3 (Reviewer's) ANCOVA analysis with baseline CFA to compare treatment effects using ITT patients

Placebo (P)		Creon 20 (C)		
MCFAD[1]	(N)	MCFAD	(N)	P-value[#] for comparing P and C
51	18	87	18	<0.0001*

1: mean of CFA at end of double blind phase; *: Significant at .05 significance level;
[#]: p-value calculated from ANCOVA model with treatment, center, treatment by center, and baseline CFA as parameters.

Table 2.2.2.2.3 indicates that the mean CFA for Creon®20 at the end of double-blind phase is significant ($p < 0.0001$) higher than that of placebo using analysis of covariance model with treatment, center, center by treatment, and baseline CFA as model parameters.

3) Subgroup analyses.

In order to assess the consistency of the treatment effect of Creon®20 over placebo across subgroups, this reviewer performed the subgroup analysis using the sponsor's general linear model on the primary endpoint (change in CFA) based upon ITT patient population. The subgroups analyzed are Gender (Male and Female), Race (Caucasian and non-Caucasian), and Age group (age # 65 and age > 65).

Gender

Table 2.2.2.2.4 presents the results of treatment efficacy comparisons for Creon®20 versus placebo by gender.

Table 2.2.2.2.4 (Sponsor's) CFA changes from open-label to double-blind treatment phases (ITT population)

Male

Open-label phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 20		Placebo		Creon 20		Placebo		Creon 20	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
88	12	88	10	54	12	84	10	-34	12	-4.0	12
										P[#] = 0.001*	

Female

Open-label phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 20		Placebo		Creon 20		Placebo		Creon 20	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
87	6	90	8	44	6	90	8	-43	6	-0.0	8
										P = 0.001*	

[#]: p-value calculated based on analysis of variance model with factors of center, treatment, and center by treatment interaction.
*: Significant at .05 significance level.

Table 2.2.2.1.4 indicates that at significance level of 0.05, the efficacy of Creon®20 is superior to that of placebo assessed by the change in CFA from the open-label phase to the double-blind treatment phase for both females and males.

Race (Caucasian and non-Caucasian)

Since al patients entered the double-blind treatment phase were Caucasian (White), no race

analysis is performed.

Age group (age # 65 and age > 65)

Since all patients entered the double-blind treatment phase were with ages not greater than 65 years old, no age-group analysis is performed.

2.2.2.2.2 Finding Remarks

- The effect of Creon®20 is consistently better than that of placebo across the five centers assessed by the change in CFA from the open label phase to the double-blind phase. The significant interaction between treatment and center is deemed as a quantitative interaction. Thus, the treatment efficacy comparison can be performed by pooling/averaging the differences of the treatment effects across the centers. The results from the sponsor's unweighted and this reviewer's weighted methods all show that the efficacy of Creon®20 is significantly better than that of placebo assessed by the change in CFA from the open-label phase to the double-blind treatment phase.
- The ANCOVA analysis using CFA at the end of the double blind phase as the dependent variable along with treatment effect, center, treatment by center, and baseline CFA as the explanatory variables, performed by this reviewer, shows that Creon®20 is superior to placebo. It indicates that the superiority of Creon®20 to placebo is not sensitive to the different analysis model.

2.2.2.3 Study CR200.0124

2.2.2.3.1 Reviewer's Statistical Analysis

In the protocol, the sponsor indicated that data for the secondary endpoints were to be summarized by treatment group comparing change from baseline. However, the sponsor did not specify what statistical methods were to be used to analyze the secondary endpoints. In addition, the sponsor also emphasized that all statistical analyses performed on the secondary endpoints were to be for exploratory purpose. Therefore, in this reviewer's statistical analysis, the primary endpoint is the focus: the change in CFA from the baseline to the double blind phase.

In order to validate the sponsor's efficacy claim, the following two analyses are performed: 1.) Exploratory analysis and 2.) Subgroup analyses. Data sets used by this reviewer's analysis were submitted by the sponsor on June 27, 2003.

1.) Exploratory analysis

As noted by this reviewer in the section of 2.2.1.3, one Creon patient whose fecal fat excreted in the single-blind placebo phase abnormally exceeded the amount of dietary fat ingested had extremely large CFA change value (122) from the single-blind placebo phase to the double-blind treatment phase. In order to assess the adequacy of including the patient with the abnormal value

in the efficacy analysis, this reviewer calculates the sample standard deviations of CFA change values separately for both treatment groups. Table 2.2.2.3.1 presents the sample standard deviations along with the sponsor's analysis results using data sets including and excluding the patient with the abnormal CFA change value 122.

Table 2.2.2.3.1 (Reviewer's) CFA change from baseline to double blind phase using ITT patient population
No patients excluded

Single-blind Placebo phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 10		Placebo		Creon 10		Placebo		Creon 10	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%) ± sd	N	CFA (%)± sd	N
56	14	50	12	68	14	87	12	12 ± 19	14	37 ± 30	12
								$P^{\#}$=0.019*			
One Patient in Creon®10 with CFA change 122 Excluded											
Single-blind Placebo phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 10		Placebo		Creon 10		Placebo		Creon 10	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)± sd	N	CFA (%) ± sd	N
56	14	57.5	11	68	14	86	11	12 ± 19	14	28.5± 14	11
								$P^{\#}$ =0.023*			

#: p-value calculated based on analysis of variance method with treatment as parameter; sd: Sample standard deviation;
*: Significant at .05 significance level.

Table 2.2.2.3.1 shows that based on the new sample standard deviation 14 for the Creon®10 group, CFA 122 is larger than the mean 28.5 plus 7 times the standard deviation 14 (ie, 28.5 + 7*14). This simple statistical analysis shows that CFA 122 may be classified as an outlier to the Creon ®10 group. In addition, as indicated above, the baseline CFA value for the patient with CFA change value 122 was –33, showing that the fecal fat excreted in the single-blind placebo phase abnormally exceeded the amount of dietary fat ingested. Since CFA 122 violated the logic of the data collection and is identified as an outlier, this data is considered carrying invalid/improper information and should be officially/formally excluded from the efficacy analysis. After excluding the abnormal CFA change value, the p-value for the treatment comparison using the sponsor general linear model was 0.023 shown by Table 2.2.2.3.1.
The general linear model employed by the sponsor only included treatment effect as the model parameter. Due to the small sample size used in the analysis, it may not have enough power to detect the violation of the normality assumption on the distribution of CFA changes. In order to avoid using the normality assumption, this reviewer performs the exact test using Mann-Whitney-Wilcoxon rank statistics on the change in CFA from baseline to the double blind treatment phase to compare the treatment effects using data set excluding the Creon patient with CFA change value 122. The exact p-value (not asymptotic one) for the two-sided Mann-Whitney-Wilcoxon rank test is 0.03.

Noted by this reviewer, only one main study was submitted by the sponsor to support the use of Creon®10 on fat absorption for patients with exocrine pancreatic insufficiency caused by chronic pancreatitis. For a single study concluded adequate in support of an effectiveness claim, the guidance for industry (1998) "Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" indicates that the presence of one or more of the following five characteristics in the study can contribute to that conclusion: 1.) Large

multi-center study, 2.) Consistency across study subsets, 3.) Multiple studies in a single study, 4.) Multiple endpoints involving different events, and 5.) Statistically very persuasive finding. For item 5, the Guidance emphasizes that in a multi-center study, a very low p-value (for example, less than .00125) indicates the result is highly inconsistent with the null hypothesis of no treatment effect. Thus, for a single study to be considered statistically persuasive in support of the efficacy claim, the p-value for the treatment comparison should be very small, like less than .00125. Clearly, although at the significance level of .05, the effectiveness of Creon®10 is significantly better than that of placebo after excluding the Creon patient with abnormal CFA change value 122, the two p-values 0.023 and 0.03 for the treatment comparisons, calculated respectively using the sponsor's general linear model and the Mann-Whitney-Wilcoxon rank test, are not low, assessed based on one single study with small sample size of 25. Finally, based on the trial design and the statistical analysis results, none of the five characteristics is found in this study. As a result, in the light of the guidance for industry (1998), the superiority of Creon®10 to placebo assessed by the change in CFA from the single blind placebo phase to the double blind treatment phase is not statistically persuasive.

Thus, from the statistical perspective, the single study did not provide substantial evidence to support the use of Creon®10 on fat absorption for patients with exocrine pancreatic insufficiency caused by chronic pancreatitis. However, it is the medical reviewer's decision to consider the capability of adopting the efficacy results shown in the support of using Creon®20 for the cystic fibrosis patients to support the use of Creon®10 to treat the patients with exocrine pancreatic insufficiency associated with chronic pancreatitis.

1) Subgroup analyses.

In order to assess the consistency of the treatment effect of Creon®20 over placebo across subgroups, this reviewer performed the subgroup analysis using the sponsor's general linear model on the primary endpoint (change in CFA) based upon ITT patient population. The subgroups analyzed are Gender (Male and Female), Race (Caucasian and non-Caucasian), and Age group (age # 65 and age > 65).

Gender

Table 2.2.2.3.4 presents the results of treatment efficacy comparisons for Creon® 10 versus placebo by gender.

Table 2.2.2.3.4 (Sponsor's) CFA changes from open-label to double-blind treatment phases (ITT population)
Male

Single-blind Placebo phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 10		Placebo		Creon 10		Placebo		Creon 10	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
52	8	50	10	62	10	85	10	10	8	35	10
										$P^{\#} = 0.043$*	

Female

Single-blind Placebo phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 10		Placebo		Creon 10		Placebo		Creon 10	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
60	6	57	3	77	6	90	3	17	6	33	3
										$P^{\#} = 0.33$	

#: p-value calculated based on analysis of variance method with treatment as parameter. *: Significant at .05 significance level.

Table 2.2.2.3.4 indicates that at significance level of 0.05, only for male subgroup, the efficacy of Creon®10 is superior to that of placebo assessed by the change in CFA from open-label phase to double-blind treatment phase.

Race (Caucasian and non-Caucasian)

Table 2.2.2.3.5 presents the results of treatment efficacy comparisons for Creon®10 versus placebo by race.

Table 2.2.2.3.5 (Sponsor's) CFA changes from open-label to double-blind treatment phases (ITT population)
Caucasian

Single-blind Placebo phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 10		Placebo		Creon 10		Placebo		Creon 10	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
54	9	46	7	67	9	84	7	13	9	38	7
										$P^{\#} = 0.09$	

Non-Caucasian

Single-blind Placebo phase (OL)				Double-blind treatment phase (DB)				Change from OL to DB			
Placebo		Creon 10		Placebo		Creon 10		Placebo		Creon 10	
CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N	CFA (%)	N
59	5	58	6	70	5	90	6	11	5	32	5
										$P^{\#} = 0.07$	

#: p-value calculated based on analysis of variance method with treatment as parameter. *: Significant at .05 significance level.

Table 2.2.2.3.4 indicates that at significance level of 0.05, for both race groups, the efficacy of Creon®10 is failed to show the superiority to that of placebo assessed by the change in CFA from open-label phase to double-blind treatment phase. However, for both Caucasian and Non-Caucasian, the effects of Creon®10 are numerically better than that of placebo.

Age group (age # 65 and age > 65)

Since almost 90% of patients entered the double-blind treatment phase were with ages not greater than 65 years old, no age-group analysis is performed.

2.2.2.3.2 Finding Remarks

- Noted by this reviewer, only one main study was submitted by the sponsor to support the use of Creon®10 on fat absorption for patients with exocrine pancreatic insufficiency caused by chronic pancreatitis. For a single study concluded adequate in support of an effectiveness claim, the guidance for industry (1998) "Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" indicates that the presence of one or more of the following five characteristics in the study can contribute to that conclusion: 1.) Large multi-center study, 2.) Consistency across study subsets, 3.) Multiple studies in a single study, 4.) Multiple endpoints involving different events, and 5.) Statistically very persuasive finding. For item 5, the Guidance emphasizes that in a multi-center study, a very low p-value (for example, less than .00125) indicates the result is highly inconsistent with the null hypothesis of no treatment effect. Thus, for a single study to be considered statistically persuasive in support of the efficacy claim, the p-value for the treatment comparison should be very small, like less than .00125. Clearly, although at the significance level of .05, the effectiveness of Creon®10 is significantly better than that of placebo after excluding the Creon patient with abnormal CFA change value 122, the two p-values 0.023 and 0.03 for the treatment comparisons, calculated respectively using the sponsor's general linear model and the Mann-Whitney-Wilcoxon rank test, are not low, assessed based on one single study with small sample size of 25. Finally, based on the trial design and the statistical analysis results, none of the five characteristics is found in this study. As a result, in the light of the guidance for industry (1998), the superiority of Creon®10 to placebo assessed by the change in CFA from the single blind placebo phase to the double blind treatment phase is not statistically persuasive.
- From the statistical perspective, the single study did not provide substantial evidence to support the use of Creon®10 on fat absorption for patients with exocrine pancreatic insufficiency caused by chronic pancreatitis. However, it is the medical reviewer's decision to consider the capability of adopting the efficacy results shown in the support of using Creon®20 for the cystic fibrosis patients to support the use of Creon®10 to treat the patients with exocrine pancreatic insufficiency associated with chronic pancreatitis.

2.2.3 Overall Conclusions and Recommendations

From the sponsor's analysis results and the finding remarks of the two Studies CRC200.0126 and CRC200.0143, the Overall Conclusions and Recommendations on the efficacy of study drug Creon®20 in treatment of patients with exocrine pancreatic insufficiency associated with cystic fibrosis disease are made as follows:

- The efficacy of Creon®20 is superior to that of placebo as assessed by the change in CFA from the open label phase to the double-blind phase. This efficacy is not sensitive to the different analysis model.
- Study CR200.0126 indicates that although the mean change in CFA for placebo in center 1 is much smaller than that of other centers, the superiority of Creon®20 to placebo still holds using patients excluding center 1. Thus, the superiority of Creon®20 to placebo is not dominated by centers with unusual data.
- Study CR200.143 indicates that the effect of Creon®20 is consistently better than that of placebo across the five centers assessed by the change in CFA from the open label phase to the double-blind phase. The significant interaction between treatment and center is deemed as a quantitative interaction. Thus, the treatment efficacy comparison can be performed by pooling/averaging the differences of the treatment effects across the centers. The results from the sponsor's unweighted method and this reviewer's weighted method all show that the efficacy of Creon®20 is significantly better than that of placebo assessed by the change in CFA from the open-label phase to the double-blind treatment phase.
- As a consequence, the efficacy of study drug Creon®20 in treatment of patients with exocrine pancreatic insufficiency associated with cystic fibrosis disease is superior to that of placebo.

From the finding remarks of Study CRC200.0124, the Overall Conclusions and Recommendations on the efficacy of study drug Creon®10 in treatment of patients with exocrine pancreatic insufficiency associated with chronic pancreatitis disease are made as follows:

- Noted by this reviewer, only one main study was submitted by the sponsor to support the use of Creon®10 on fat absorption for patients with exocrine pancreatic insufficiency caused by chronic pancreatitis. For a single study concluded adequate in support of an effectiveness claim, the guidance for industry (1998) "Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" indicates that the presence of one or more of the following five characteristics in the study can contribute to that conclusion: 1.) Large multi-center study, 2.) Consistency across study subsets, 3.) Multiple studies in a single study, 4.) Multiple endpoints involving different events, and 5.) Statistically very persuasive finding. For item 5, the Guidance emphasizes that in a multi-center study, a very low p-value (for example, less than .00125) indicates the result is highly inconsistent with the null hypothesis of no treatment effect. Thus, for a single study to be considered statistically persuasive in support of the efficacy claim, the p-value for the treatment comparison should be very small, like less than .00125. Clearly, although at the significance level of .05, the effectiveness of Creon®10 is significantly better than that of placebo after excluding the Creon patient with abnormal CFA change value 122, the two p-values 0.023 and 0.03 for the treatment comparisons, calculated respectively using the sponsor's general linear model and the Mann-Whitney-Wilcoxon rank test, are not low, assessed based on one single study with small sample size of 25. Finally, based on the trial design and the statistical analysis results, none of the five characteristics is found in this study. As a result, in the light of the guidance for

industry (1998), the superiority of Creon®10 to placebo assessed by the change in CFA from the single blind placebo phase to the double blind treatment phase is not statistically persuasive.

- As a result, from the statistical perspective, the single study did not provide substantial evidence to support the use of Creon®10 on fat absorption for patients with exocrine pancreatic insufficiency caused by chronic pancreatitis. However, it is the medical reviewer's decision to consider the capability of adopting the efficacy results shown in the support of using Creon®20 for the cystic fibrosis patients to support the use of Creon®10 to treat the patients with exocrine pancreatic insufficiency associated with chronic pancreatitis.

3.0 LABELING RECOMMENDATION ON THE INDICATION USAGE

- ✓ From the statistical perspective, Creon® 20 Minimicrospheres® Capsules are indicated for adult and pediatric patients with exocrine pancreatic insufficiency as is often associated with cyctic fibrosis.

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/s/

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