CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-725

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
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Reviewer Name	Ethan D. Hausman, MD Clinical Reviewer, DGP
Through	Joanna Ku, MD Acting Team Leader, DGP
Established Name	Pancrelipase Delayed-Release Capsules
(Proposed) Trade Name	Creon
Therapeutic Class	Pancreatic Enzyme Product
Applicant	Solvay Pharmaceuticals, Inc
Priority Designation	Priority Review
Formulation	For oral administration
Dosing Regimen	Not to exceed 2,500 lipase units/kg/meal [10,000 lipase units/kg/day] or 4,000 lipase units/gram fat ingested/day
Indication	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis and other conditions
Intended Population	Patients with exocrine pancreatic insufficiency

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Standard and Non-Standard Abbreviations used in this Document

Absolute Neutrophil Count	ANC
Adverse Event	AE
Application Integrity Policy	AIP
Active Pharmaceutical Ingredient	API
Chronic Pancreatitis	CP
Clinical Laboratory Tests	Labs
Coefficient of Fat Absorption	CFA
Coefficient of Nitrogen Absorption	CNA
Complete Response	CR
Currently Marketed Product	CMP
Cross-Over	CO
Cystic Fibrosis	CF
Cystic Fibrosis Foundation	CFF
Division of Scientific Investigation	DSI
Electrocardiogram	ECG
Exocrine Pancreatic Insufficiency	EPI (also Pancreatic Exocrine Insufficiency→PEI)
Federal Register	FR
Fibrosing Colonopathy	FC
Food and Drug Administration	FDA
Full Analysis Population	FAP
Gastrectomy	GY
Integrated Summary of Safety	ISS
Intent-To-Treat	ITT
Investigational New Drug	IND
Lipase Units	Lu
Medical Dictionary for Regulatory Activities	MedDRA
Microspheres	MS
Minimicrospheres	MMS
New Drug Application	NDA
Not Approved	NA
Pancreatic Enzyme Product	PEP
Pancreatectomy	PY
PEPs other than Creon TbMP/CMP	Other PEP
Randomized, Double-Blind Placebo-Controlled	RDBPC
Serious Adverse Event	SAE
To-Be-Marketed Product	TbMP
Treatment Control	TC
United States	US
US Pharmacopeia	USP
World Health Organization Adverse Reactions Terminology	WHOART

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This document reviews the safety and efficacy of a 3-week, randomized, double-blind, placebo-controlled clinical study of the to-be-marketed (TbMP) formulation of Creon (Pancrelipase) Delayed-Release Capsules in 32 patients with exocrine pancreatic insufficiency (EPI) due cystic fibrosis (CF), ages 12 through 43 years (S245.3.126; the Pivotal Study).

Based on comparisons of safety and efficacy, defined as mean change in 72-hour coefficient of stool fat absorption (CFA) with Creon treatment compared to CFA with placebo treatment, sufficient clinical information has been provided to recommend approval for the indication "treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions."

Creon and other pancreatic enzyme replacement products (PEPs) are associated with an increased risk fibrosing colonopathy. This risk, and the remote risk of porcine virus transmission, necessitates the use of a Risk Evaluation and Mitigation Strategy (REMS) and a Medication Guide (Med Guide).

In conclusion, this Reviewer recommends Approval for the to-be-marketed formulation of Creon (Pancrelipase) Delayed-Release Capsules for treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

1.2 Risk Benefit Assessment

The Pivotal Study was a 3-week, multi-center, randomized, double-blind, placebo-controlled, cross-over (CO) study of 32 patients with CF ages 12 to 43 years. The study was performed with the to-be-marketed product (TbMP; hereafter Creon). CF diagnosis was by iontophoresis or genetic testing. Patients must have been on another PEP at a stable dose for at least 3 months prior to Pivotal Study entry. Enrollees needed evidence of EPI, proven by a documented CFA <70% or fecal elastase <50 ug/gram stool in the prior year.

Creon dose was 4,000 USP Lipase units (Lu) per gram of dietary fat (Lu/gram fat/day) based on a diet that met the caloric requirements of each patient, with 40% of calories derived from fat and a minimum of ≥100 gram fat/day diet. Patients were randomized 1:1 to either Creon→Placebo or Placebo→Creon treatment groups. Each CO treatment period was up to 7 days. The procedure for 72-hour stool collections for CFA analyses began on the evening of Day 2 of each CO treatment period. Treatment effect for each patient was defined as CFA obtained during Creon treatment (Creon CFA) minus CFA obtained during Placebo treatment (Placebo CFA); patients served as their own control.

Efficacy was defined as the mean change in CFA [Creon minus Placebo] for the full analysis population (FAP), i.e., all patients who received ≥1 randomized dose who also had CFA assessments during both Creon and Placebo treatment (N=31). A sensitivity analysis was performed on a modified FAP that excluded two patients where data quality was not assured (N=29).

- Mean change in CFA for the FAP was 39% (95% C.I. 32, 46); $p<0.001$ using ANOVA modeling with treatment, sequence, and cross over period as fixed effect and patient within sequence as a random effect.

- Mean change in CFA for the modified FAP was 41% (95% C.I. 34, 47); $p<0.001$ using similar ANOVA modeling.

The clinical and statistical review team concludes these results are clinically meaningful and statistically significant. Secondary efficacy endpoints were not validated and recognized clinical endpoints, were not used for determining efficacy or inform labeling, and are not presented here.

Short-term safety assessments are based on the 3-week Pivotal Study. There were no deaths in the Pivotal Study. One patient was discontinued from the study after completing Creon treatment, due to weight loss >5% that had occurred within 3 months of Screening, which was a violation of entry criteria. Two SAEs, duodenitis and gastritis, were reported in one patient 16 days after Creon treatment; the relationship of these SAEs to Creon can not be determined. Noteworthy clinical laboratory findings were restricted to decreased neutrophil counts in three patients with Creon treatment compared to the Screening visit or Placebo treatment (one of these patients experienced transient decrease in neutrophil counts that met the clinical definition of neutropenia while he was receiving Creon and a macrolide antibiotic). No case of decreased neutrophil counts was associated with clinical sequelae. There were no other clinically meaningful clinical laboratory findings, and there were no clinically meaningful trends in vitals signs. There were no cases of hyperuricemia or hyperuricosuria. There were no documented cases of fibrosing colonopathy (FC) in the Pivotal Study which is not unexpected due to the short duration of exposure (5 to 7 days) and lack of monitoring for FC (i.e., surveillance colonoscopy and biopsy).

The submission also contains clinical information from 37 studies of the currently-marketed-product (CMP) and 22 studies of non-TbMP/non-CMP PEPs (e.g., other PEPs) submitted in the Integrated Safety Summary (ISS) update, as well as approximately 16 years of CMP post-marketing data. The safety information from these data were similar to published data in the medical literature, with most adverse events due to primary disease, complications of primary disease, and other unrelated causes. This Reviewer felt that the following findings should be included in the labeling in the post-marketing experience adverse reactions section. The most serious adverse events reported were fibrosing colonopathy, distal intestinal obstruction syndrome (DIOS), severe allergic reactions including anaphylaxis, asthma, hives and pruritus, and recurrence of pre-existing carcinoma. The most commonly reported adverse events were gastrointestinal disorders, including abdominal pain, diarrhea, flatulence, constipation and nausea, and skin disorders including pruritus, urticaria and rash. These safety data may be used

to support safety of the PEP drug-class, and in general, these products have a well defined and favorable risk-benefit profile in exocrine pancreatic insufficiency.

This conclusion is consistent with the Agency's prior regulatory determination that a considerable body of evidence suggests that replacement of pancreatic enzymes has clinical benefit for patients with EPI due to cystic fibrosis and chronic pancreatitis (69 FR 23410), which also allowed NDA 20-725 and other porcine-derived PEPs to qualify for consideration under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (FDCA).

On consideration of available information, including studies of the TbMP in patients with CF-related EPI 12 years and older, an extensive literature base describing a favorable risk:benefit balance for long-term use of non-TBMP PEPs in adult and pediatric patients with CF- and chronic pancreatitis-related EPI, and widely implemented dose guidelines (the Cystic Fibrosis Foundation Guidelines) for patients with CF-related EPI based on studies performed with other PEPs, the Pediatric Review Committee (PeRC) recommended to the Division of Gastroenterology Products (DGP) that safety and efficacy in children could be extrapolated to include an indication to treat EPI in children of all ages. This finding would not exempt the Applicant from development of age appropriate formulations under PREA.

1.3 Recommendations for Postmarketing Risk Management Activities

A Medication Guide (MedGuide) was submitted and reviewed as part of a Risk Evaluation and Mitigation Strategy (REMS) to help ensure adequate communication of the risks of fibrosing colonopathy and the remote risk of porcine virus transmission. Risk for transmission of porcine viruses and a risk-mitigation strategy was discussed at a meeting of the Antiviral Drugs Advisory Committee (AVAC) on 2-December-2008. The AVAC concluded that Creon and other porcine derived PEPs carry a remote but real risk for transmission of potential pathogenic porcine viruses—that is, cross-species infection. The submitted REMS and MedGuide address the risk of fibrosing colonopathy and porcine virus transmission.

The recommended language for the Approval Letter is as follows (see final Approval Letter):

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS (REMS)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, FDA has determined that a REMS is necessary for Creon (pancrelipase) Delayed-Release Capsules and other porcine-derived pancreatic enzyme products (PEPs) to ensure that the benefits of the drug outweighs the risk of fibrosing colonopathy with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients. The REMS, once approved, will create enforceable obligations.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Creon (pancrelipase) Delayed-Release Capsules poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Creon (pancrelipase) Delayed-Release Capsules. FDA has determined that Creon (pancrelipase) Delayed-Release Capsules is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Creon (pancrelipase) Delayed-Release Capsules. In addition, patient labeling could help prevent serious adverse effects related to the use of the product. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Creon (pancrelipase) Delayed-Release Capsules.

Your assessment of the REMS should include an evaluation of:

a. Patients' understanding of the serious risks of Creon (pancrelipase) Delayed-Release Capsules
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

1. Deferred requirement for development of an age appropriate formulation for Creon (pancrelipase) Delayed-Release Capsules: Develop an age appropriate formulation to allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Submit a supplement for an age appropriate formulation by December 31, 2010.

FDA is waiving the pediatric study requirement for ages 0 months to 1 month because necessary studies are impossible or highly impracticable. This is because patients are not usually diagnosed below 1 month of age, so there would not be enough eligible patients in this age range to study.

This product is appropriately labeled for use in all relevant pediatric populations. Therefore, no additional pediatric studies are needed at this time.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

FDA has determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of fibrosing colonopathy and the unexpected serious risk of transmission of viral disease to patients. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following studies:

2. A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Creon (pancrelipase) Delayed-Release Capsules in the US and to assess potential risk factors for the event.

   The timetable you submitted on April 17, 2009 states that you will conduct this study according to the following timetable:

   Final Protocol Submission: **by June 20, 2010**
   Study Completion Date: **by January 1, 2021**
   Final Report Submission: **by June 20, 2021**

3. A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Creon (pancrelipase) Delayed-Release Capsules.

   The timetable you submitted on April 17, 2009 states that you will conduct this study according to the following timetable:

   Final Protocol Submission: **by June 20, 2010**
   Study Completion Date: **by January 1, 2021**
   Final Report Submission: **by June 20, 2021**

1.4 Recommendations for other Post Marketing Study Commitments

The following post marketing study commitments (PMCs) will also be performed.

4. Solvay commits to complete Study S245.3.124, a multi-center, randomized, double-blind, placebo-controlled trial of the safety and effectiveness of Creon (pancrelipase) Delayed-Release Capsules in patients 18 years and older with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy. The study will have an open-label 6-month extension.

   Final Report Submission: by September 20, 2009

5. Solvay commits to perform routine monitoring of the enveloped viral load entering the manufacturing process. The control strategy will include the selection of human pathogenic enveloped viruses for monitoring by qPCR together with action limits and specifications.

   Final Protocol Submission: by October 20, 2009
   Final Report Submission: by October 20, 2010

6. Solvay commits to continue developing sensitive qPCR assays that provide adequate assurance that process capability for the inactivation of non-enveloped viruses is not exceeded. The revised assay and assay validation data, together with new action limits, will be submitted to the Agency.

   Final Report Submission: by October 20, 2009

7. Solvay commits to develop and implement specifications for infectious porcine circoviruses (PCV) 1 and 2 in the drug substance. The proposed methods, including relevant method validation, will be submitted to the Agency.

   Final Report Submission: by October 20, 2010

8. Solvay commits to assess the risk to product quality associated with porcine hokovirus, and submit a control strategy for mitigating this risk to product quality.

   Final Report Submission: by October 20, 2009

9. Solvay commits to revise the acceptance criteria for the viral infectivity tests for swine vesicular disease virus (SVDV), encephalomyocarditis virus (EMCV) and porcine rotavirus (Rota) to "none detected."

   Final Report Submission: by July 1, 2009

10. Solvay commits to provide detailed plans for its animal disease surveillance program and continued risk assessment evaluation for source animals. The proposed plans will include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these plans will be implemented.

    Final Report Submission: by October 20, 2009

11. Solvay commits to assess the risk to product quality due to the potential infection of swineherds with parasites.

    Final Report Submission: by October 20, 2009

12. Solvay commits to provide a detailed description of its plans for preventing cross-contamination with material from other species, particularly with ruminant tissues.

    Final Report Submission: by October 20, 2009

2 Introduction and Regulatory Background

2.1 Product Information

The investigational agent studied in the application is the to-be-marketed (TbMP) formulation of Creon (Pancrelipase Delayed-Release Capsules).. PEPs are derived from porcine pancreata. PEPs contain varying amounts of lipases, amylases, and proteases, which break down nutrient lipids, carbohydrates, and proteins for absorption. Creon is intended to provide an exogenous source of orally administered pancreatic enzymes to adults and children with EPI from a variety of causes, such as CF and chronic pancreatitis (CP). Dose is administered as lipase units per kilogram body-weight per day (Lu/kg/day) or lipase units per gram of fat ingested per day (Lu/gram fat/day). The formulation of Creon used in the Pivotal Study was provided as gelatin capsules for oral administration.

The Applicant (Solvay) originally intended to market the product under the trade name Creon ® 6, 12, and 24 capsules, which would contain 6,000, 12,000, and 24,000 Lu/capsule, respectively. The Division of Medication Error and Prevention Analysis (DMEPA) review determined that the trade name Creon is acceptable but that modifier numbers or letters after the "®" mark are not acceptable. The reader is directed to the final DMEPA review for detailed comments (D Hamilton-Stokes).

2.2 Tables of Currently Available Treatments for Proposed Indications

PEPs have been marketed in the United States (US) without NDAs since before passage of the Food, Drug and Cosmetic Act of 1938. PEPs are currently widely available in the US as

nutritional supplements and are produced and distributed by a number of manufacturers. PEPs are available as enteric coated/delayed-release and non-enteric coated formulations. FDA has determined that due different manufacturing raw material sources and different manufacturing processes (including extraction methods), and that they may contain different excipients—unless comparability has been established, the manufacturing products from different manufacturers are not comparable, and therefore not interchangeable. Seven manufacturers/sponsors have one or more products under IND study or NDA review. An additional product was approved under NDA in the 1990, but is not currently in distribution in the US (Table 1).

Table 1: List of PEP Products Under IND Study or NDA Review (Competing or Potentially Competing Products).

IND	NDA	Product	Manufacturer/Sponsor
47,546	20-725	Creon minimicrospheres; Delayed-Release	Solvay
(b) (4)			
70,563	22-210	Zentase; Delayed-Release	Eurand
(b) (4)			
(b) (4)			
*	20-580	Cotazym	Organon

n/a-NDA not submitted
*Approved under NDA in 1996; Not currently marketed in US.

After April 2010, any PEP that is marketed in the US without prior receipt of marketing approval under an NDA will be considered misbranded and subject to regulatory action.

2.3 Availability of Proposed Active Ingredient in the United States

Creon brand capsules first became commercially available in the US in 1987 as Creon Microsphere® (MS) capsules. In 1993, the Applicant introduced Creon Minimicrospheres (MMS) to replace the MS form. The CMP is currently commercially available in the US as a nutritional supplement. The Applicant's application states the CMP has marketing authorizations in approximately 76 countries worldwide. Neither the CMP nor the TbMP has received prior US marketing authorization under an NDA.

The active pharmaceutical ingredient (API) in the TbMP is pancrelipase. Please refer to the review from the Division of Therapeutic Proteins for a discussion of the API.

2.4 Important Safety Issues With Consideration to Related Drugs

Two established safety issues with PEPs are fibrosing colonopathy (FC) and hyperuricemia. Because Creon is a porcine-derived product there is also a risk for transmission of adventitious virus such as porcine parvovirus.

Fibrosing colonopathy (FC) is associated with prolonged high-dose PEP administration (>6000 Lu/kg/meal or >24,000 Lu/kg/day) particularly in younger patients.[1] This serious complication can progress to acute abdomen and necessitate surgical resection of affected intestine. Therefore, monitoring for FC in PEP clinical development programs is relevant to the assessment of safety for this class of medications. No instances of fibrosing colonopathy (FC) were reported in the Pivotal Study or in the ISS. Limitations in the surveillance program are noted below:

- FC is a histopathologic diagnosis; however, surveillance colonoscopy and biopsy were not performed in the Pivotal Study.
- FC is a symptomatically severe and acute process, but literature suggests it may have a chronic indolent course; therefore, while severe cases may not have come to clinical attention during the Pivotal Study, incipient or indolent cases might not have been recognized.
- The intended dose of Creon used in the study was around the upper limit recommended to decrease risk of FC. While several patients received >10% above the intended dose, duration exposure (5 to 7 days) may not have been sufficient to precipitate FC.[2, 3, 4, 5]
- The study population may not have been large enough to detect an FC safety signal.

This Reviewer concludes that since the study was not designed to refute the risk of FC, labeling should prominently address the risk of FC.

PEPs have high purine content and patients may develop hyperuricemia.[6] No cases of hyperuricemia were reported. Risk of hyperuricemia will be discussed in labeling.

The risk of adventitious viruses and risk mitigation strategies for these viruses is addressed in the review from the Division of Therapeutic Proteins and was the subject of a meeting of the Antiviral Drugs Advisory Committee Meeting on 2-December-2008.

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1 FitzSimmons SC, Burkhart GA, Borowitz D, Grand RJ. High-Dose Pancreatic-Enzyme Supplements and Fibrosing Colonopathy in Children with Cystic Fibrosis. NEJM. 1997. 336(18): 1283-1289.

2 Borowitz D, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. J Pediatric Gastroenterology and Nutrition. 2002. 35:246-259.

3 Borowitz, D, Grand RJ, Durie PR, and the Consensus Committee, Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127:681-684.

4 Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs. April 2006. http://www.fda.gov/CDER/guidance/6275fnl htm (hereafter refered to as the PEP Guidance)

5 Stallings VA, Stark LJ, Robinson KA, Feranchak AP, et. al., Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review. J Am Diet Assoc. 2008; 108: 832-839.

6 Davidson GP, Hassel FM, Crozier, D. Corey M, Forstner GG. Iatrogenic hyperuricemia in children with cystic fibrosis. J Pediatrics. 1978. 93(6):976-978.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Creon Minimicrospheres (Creon MMS) first became available in the US in 1993. Since 1993, the currently-marketed-product (CMP) has been in continuous distribution. The Applicant intends to replace CMP with the to-be-marketed product (TbMP).

The original IND [for the CMP] was opened in March 1995 (IND 47,546) and the original NDA (NDA 20-725) was received in July 1997. In September 1997, CDER determined that the Applicant's facilities in Marietta GA and Baudette MN were not in compliance with the Agency's Application Integrity Policy (AIP), and review of the NDA was suspended.[7] On April 9, 2003 FDA resumed review of the NDA after the Applicant prepared and implemented a Corrective Operation Plan, which appeared to provide sufficient safeguards to preclude future wrongful acts and non-compliance with regulatory requirements.

Review of the original NDA for Creon was completed in October-2003. The NDA application was not approved. Summaries of study design and efficacy results from the three studies submitted in support of efficacy are summarized below:

- Study S223.3.101, performed with Creon CMP, was a short-term, randomized, double-blind, placebo-controlled, treatment-withdrawal trial of 38 children with CF, ages 7 through 17 years. Mean dose was 7,651 Lu/kg/day. CFA was 31% higher (p-value < 0.001) in the Creon CMP group (N=18) compared to the placebo group (N=20). These findings show a statistically significant and clinically meaningful benefit of Creon CMP treatment in pediatric patients with EPI due to CF, ages 7 years and older.

- Study S223.3.102, performed with the Creon CMP, was a short-term, randomized, double-blind, placebo-controlled, treatment withdrawal trial of 36 adults with CF, ages 18 through 53 years. Mean dose was 4,537 Lu/kg/day. CFA was 35% higher (p-value < 0.001) in the Creon CMP group (N=18) compared to the placebo group (N=18). These findings show a statistically significant and clinically meaningful benefit of Creon CMP treatment in adult patients with EPI due to CF, ages 18 years and older.

- Study 223.2.01, performed with the Creon CMP, was a short-term, randomized, double-blind, placebo-controlled trial of 27 adults with CP, ages 38 through 74 years. Mean dose was 125,000 Lu/day (estimated 1,860 Lu/kg/day). CFA was 16% higher (p-value 0.0185) in the Creon CMP group (N=12) than the placebo group (N=14). The clinical review team concluded these findings were statistically meaningful and showed a trend toward clinically meaningful benefit in adults with EPI due to CP.

- In these three studies the short-term safety findings were generally consistent with published literature. Most adverse events were related to primary disease, complications of primary disease, or unrelated causes and were not apparently attributable to Creon treatment.

7 56 FR46191

The Not Approved (NA) decision was based on inadequate Chemistry, Manufacturing and Control (CMC) issues. Also, while efficacy and short-term safety of the CMP were demonstrated, comparability of the product used in those trials (Creon CMP) to the TbMP was not addressed in the submission. The Agency determined that safety and efficacy of the TbMP needed to be demonstrated in a clinical study of the TbMP or through a bridging study (e.g., demonstration of similar *in vivo* gut-lipase bioavailability of CMP and TbMP).

The Applicant submitted a Complete Response (CR) in November 2006 (e.g., the 2006 CR) to address the deficiencies that resulted in the prior non-approval. The 2006 CR included three new clinical studies of CMP; one of which attempted to bridge CMP to TbMP.

- S248.3.003: This was a short-term open-label, single arm study of CMP in infants up to 2 years old with CF, with patients serving as their own controls; N=12. Dose was 2,000 Lu/gram of fat intake. The primary efficacy comparison was mean change in CFA during CMP treatment compared to non-treatment (Baseline). The mean change in CFA was 27% (95% C.I. [12.9, 40.4]). The statistical reviewer concluded that statistical inferences could not be made due to the small study size. The clinical review team concluded the results were clinically meaningful, but noted that this study was performed with the CMP, not the TbMP.

- S245.3.115: This was a short-term, multi-center, randomized, double-blind, non-treatment (placebo) run-in, parallel-group study of CMP in adults with chronic pancreatitis (N=35) and pancreatectomy (N=59) with patients serving as their own controls. After non-treatment run-in (Baseline), one of three randomized treatments was provided: Placebo, low-dose CMP (60,000 Lu/day), or high-dose CMP (120,000 Lu/day). The primary efficacy comparison was mean change in CFA for each treatment group compared to Placebo (non-treatment) Baseline. Mean change for the Placebo group was 4% (mean Baseline CFA 55%), mean change for the low-dose group was 11% (mean Baseline CFA 67%), and mean change for the high-dose group was 16% (mean Baseline CFA 68%). Compared to the Placebo group, mean CFA change for the low-dose group was 7%, and mean CFA change in the high-dose group was 12%. The mean change in CFA compared to Placebo was notably less than 30% and the clinical review team was unable to determine if the results were clinically meaningful. Additionally, statistical inferences could not be made due to an interim efficacy analysis that was performed without pre-specified modification of the statistical plan.

- S245.2.003 (i.e., Bridging Study): This was a short-term, single-center, randomized, double-blind, cross-over, duodenal intubation bioavailability study in 15 adults with chronic pancreatitis, intended to establish comparability of *in vivo* gut lipase activity between the CMP and TbMP. Each patient underwent an overnight fast, followed by a meal and a dose of CMP or TbMP (60,000 Lu). Patients then underwent continuous duodenal aspiration for 3 hours. Nine patients completed the study. The clinical pharmacology reviewer determined that high inter-patient variability of gut lipase activity with both CMP and TbMP rendered the study unreliable for establishing comparability. Additionally, the Division of Scientific Investigation (DSI) report states that in multiple

instances the identity of the administered product could not be confirmed. This Reviewer concludes that the results of this study neither support nor refute comparability.

- The short-term safety findings in these studies were generally consistent with published literature. Most adverse events were related to primary disease, complications of primary disease, or unrelated causes and were not apparently attributable to Creon treatment.

Since short-term safety and efficacy were not yet demonstrated in clinical trials of the TbMP and since conclusions regarding comparability of gut lipase bioavailability of CMP to TbMP could not be made, the Agency was not able approve the TbMP product. Therefore, the 2006 CR received an Approvable Action. In the Agency's letter to the Applicant that described the issues that precluded approval, the Agency recommended clinical trials with the TbMP, as well as requiring additional CMC data relating to manufacturing and viral transmission controls.

The Applicant submitted the current CR in June 2008 (e.g., the 2008 CR). The 2008 CR contains clinical information from a single adequate and well-designed trial of TbMP in 32 patients with CF, ages 12 to 43 years (Study S245.3.126, the Pivotal Study). The submission also contains clinical information from 37 studies of CMP and 22 studies of non-TbMP/non-CMP PEPs (other PEPs) submitted with the Integrated Safety Summary (ISS), as well as approximately 16 years of CMP post-marketing data. The safety information from these 59 studies of non-TbMP formulations was similar to published data, with most adverse events due to primary disease, complications of primary disease, or unrelated causes. This Reviewer concludes these safety data support safety of the drug class and the TbMP.

The current CR was received 19-June-2008 and the original PDUFA goal date was 20-December-2008. A major amendment was received 8-December-2008 and the revised PDUFA goal date was 20-March-2009.

2.6 Other Relevant Background Information

PEPs have been available in the US since before the enactment of the Food, Drug, and Cosmetic Act of 1938, and prior to the Drug Efficacy Study Implementation (DESI) requirements of 1962, and the majority of currently available PEPs have not been developed under a clinical framework that would support an NDA and, as of October 2008, have not been submitted for NDA review. The one PEP approved under NDA, Cotazym, is not currently marketed in the US, and all PEPs currently available in the US are marketed as nutritional supplements. Of currently available PEPs, various dosage forms, including uncoated tablets, powders, capsules, enteric-coated tablets, and encapsulated enteric-coated micro-spheres are available which are not clinically interchangeable.

In the late 1980s and early 1990s, FDA assessed the appropriateness of marketing PEPs as over-the-counter drugs. As part of this endeavor, FDA evaluated the safety and effectiveness of then marketed PEPs, and noted the following issues across most or all products:

- Variation in bioavailability among similar dosage forms between manufacturers.

- Variation in bioavailability within the same product from one manufacturer (e.g., lot to lot and within lot variability).

- Patients treated with PEPs, such as patients with EPI due to cystic fibrosis (CF), require chronic medical monitoring.

FDA determined that these issues could have a meaningful effect on safety and efficacy, necessitating new drug review of each product in order to standardize enzyme bioactivity. FDA also determined that since continuous physician monitoring of patients would be necessary for the safe and effective use of PEPs, these products should be available by prescription only. FDA announced these decisions in the Federal Register on 28-April-2004, and subsequently published a guidance in the Federal Register of 14-April-2006 (i.e., the PEP Guidance), intended to provide regulatory assistance to manufacturers that plan to submit NDAs for PEP therapies. This Reviewer notes the PEP Guidance was intended to address development of animal-derived PEPs rather than PEPs developed through other methods such as cell-line derived (i.e., recombinant) products.[4]

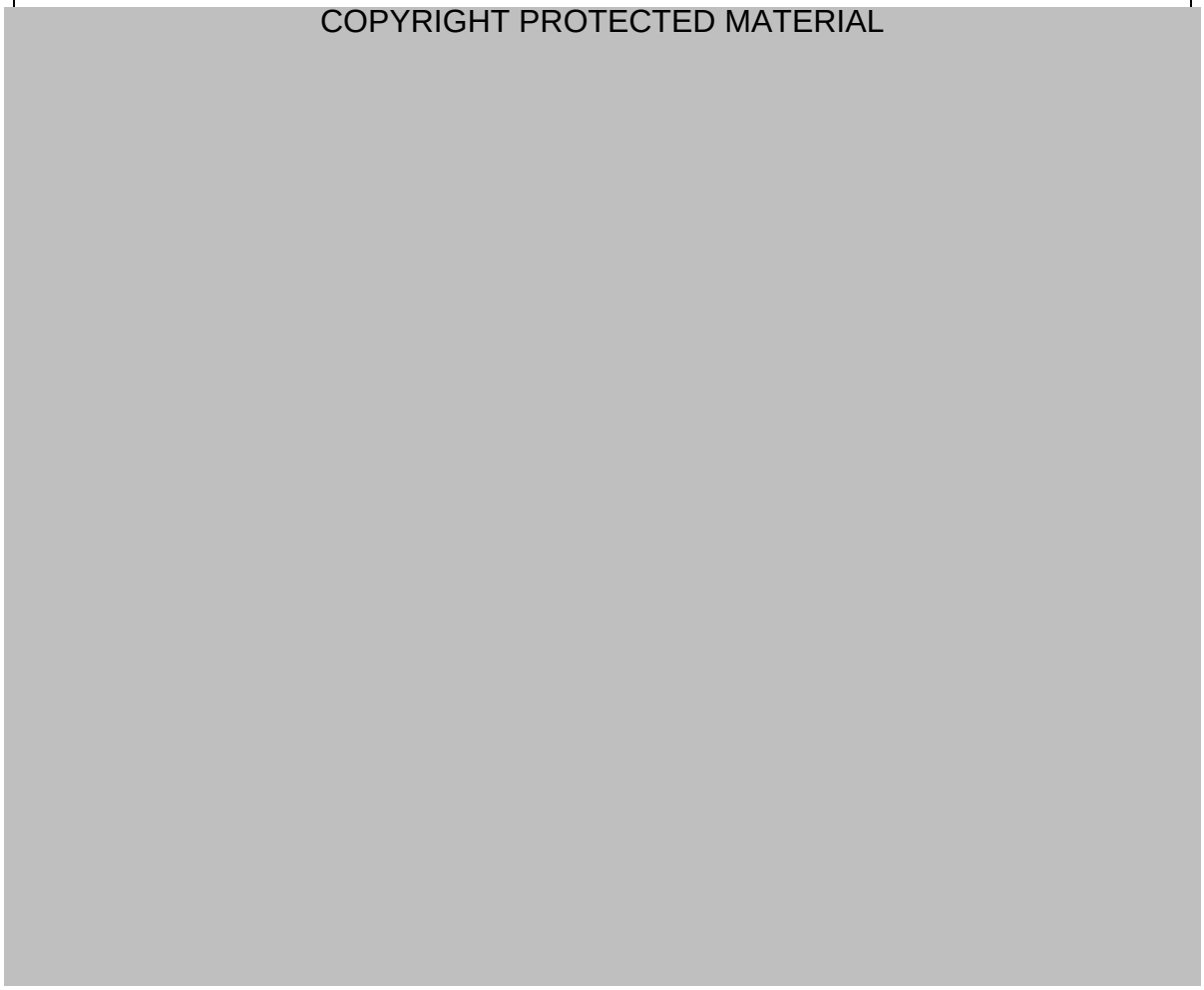
The 2004 FR notice also advised the public that FDA intended to exercise enforcement discretion until 28 April 2008. As the 2008 deadline approached, manufacturers expressed that they were not able to meet the original deadline. FDA determined that a substantial number of manufacturers who were otherwise believed to be pursuing due diligence for their product development plans would not be able to meet the 2008 deadline set forth in the 2004 FR notice requirements. The 2008 deadline was later extended to avoid an interruption in availability, and in October 2007 FDA announced its intent to continue exercising enforcement discretion until 28 April 2010 for products under active IND on or before 28 April 2008 and under NDA on or before 28 April 2009.

As noted in the PEP Guidance, PEPs have a generally well-described risk profile in children and adults with EPI, are well-tolerated, and the incidence of FC has decreased with implementation of Cystic Fibrosis Foundation (CFF) dose guidelines.[4, 6, 7] As noted in section 2.5 of this review, risks associated with PEP use include FC, hyperuricemia, and a theoretical risk of porcine virus transmission with potential for clinical illness.

On performance of an exhaustive literature search, no adequate long-term studies establishing long-term positive effects of PEP treatment on growth in children with CF-related EPI were identified. However, this Reviewer notes there is considerable evidence of the effect of positive effects of early diagnosis and multi-modal interventions including aggressive nutritional support in tandem with PEP therapy, pulmonary care, and antibiotic therapy. This positions is reflected in the 2006 Cystic Fibrosis Foundation Annual report indicating that median survival of CF patients has increased from approximately 25 years in 1986 to approximately 37 years in 2006 (Figure 1).[8,9]

8 Cystic Fibrosis Foundation 2007 Annual Report. Page 2.
http://www.cff.org/UploadedFiles/aboutCFFoundation/AnnualReport/2007-Annual-Report.pdf
9 Cystic Fibrosis Foundation 2007 Patient Registry 2006. Annual Data Report to the Center Directors, Bethesda, MD. www.cff.org.

Figure 1: Median Survival of CF Patients[8,9]



Additionally, recently published evidence based review concludes that PEPs are associated with improved nutrition and that improved nutrition is associated with improved respiratory function and growth indices such as weight-for-height percentiles, and that these improvements are associated with improved pulmonary function and survival in adults and children.[5]

Additional references addressing the use of PEPs in patients with EPI is located in Appendix 9.1 of this review.

In summary, FDA accepts that the above data supports an overall positive risk-benefit profile for the use of PEPs in the treatment of EPI. FDA also believes that the weight of this prior clinical evidence is sufficient to allow the safety and efficacy of a candidate PEP drug to be demonstrated by a single adequate and well-controlled, short-term study using CFA as primary efficacy endpoint. However, the following regulatory issues identified by FDA, as stated in the PEP Guidance, are to be addressed for any marketed PEP:[4]

- To comply with the Pediatric Research Equity Act of 2003 (PREA), PEP applications must contain data that are adequate to assess the safety and effectiveness of the PEP for the claimed indications in each of the appropriate pediatric subgroups (newborns, infants, children and adolescents). Studies may not be needed in each pediatric age group if data from one age group can be extrapolated to another. As with the use of adult data, the extrapolation can be supplemented with data to define dosing and safety for the relevant age groups.

- As with other animal-derived products, Applicants must perform full viral risk assessments and must show removal and/or inactivation of viral agents per the International Council on Harmonization (ICH) standards document Q5A.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The design of Pivotal Study is generally adequate. The study report and datasets were substantially complete and allowed substantive review. On review of a single interim Blinded Data Review (BDR) and its supporting documents, the clinical and statistical review teams concluded that the blind was not broken. No references to an independent data safety monitoring board (DSMB) were located in the study report; however, a representative of the Applicant's Quality Assurance Department was authorized to audit each site for adherence to regulatory requirements. Data quality issues with two patients and results of the Division of Scientific Integrity (DSI) inspection are discussed in section 3.2 of this document.

Except for a single new study with data integrity issues (S245.3.119) that was performed in Russia, the safety information from the remaining 59 studies of non-TbMP formulations was reviewed previously (Ethan D. Hausman MD August 16, 2007 and Fathia Gibril MD December 9, 2003). Safety findings were similar to published literature with most deaths and AEs related to primary diseases such as CF and pancreatic carcinoma, complications of primary diseases such as infection, or unrelated causes such as trauma.

3.2 Compliance with Good Clinical Practices

The Pivotal Study began on 15-November-2007 and the last patient completed treatment on 6-March-2008. The Applicant states the Pivotal Study was performed under current GCP standards.

The Applicant certifies that no debarred investigators participated in the Pivotal Study. The Pivotal Study appears to have been performed in accordance with acceptable ethical standards with collection of informed consent from patients or their parents/guardians, adequate safety monitoring, and recording of clinical information in case report forms (CRFs).

The Applicant reported data quality/integrity concerns from one site (site 23, two patients). Both patients were dosed according to the principle investigator's (PIs) judgment rather than by pre-specified dose and the pre-specified meal plan was not provided. Other issues identified at this site include:

- Adverse events recorded by ancillary staff were not assessed during the course of the study by the PI
- Lack of documentation of delegated of responsibilities
- Lack of confirmation of review of source documentation
- Lack of uniform source documentation at the site—three types of source documentation
- "Recording discrepancies" (not otherwise defined) in all source documents

This review team concluded that clinical data from these patients were unreliable. Review of the clinical information from other study sites revealed no other notable data quality issues. The problematic data could be isolated and did not preclude assessment of the remaining data. These conclusions are supported by DSI inspection (Khairy Malek, MD 3-December-2008). Therefore, this Reviewer concludes that the overall study was conducted in adherence to GCP.[10]

3.3 Financial Disclosures

A FDA form 3454 was submitted and reviewed and no financial interests were disclosed.

Curricula vitae (CV) for the 10 primary investigators were reviewed. Eight CVs contained listings of grants/other monies received for related activities such as speaking engagements. None of these eight CVs lists the Applicant as a funding source, but in some cases the funding source for individual projects was not identified. Two CVs did not list funding sources for research or related activities. The Applicant was not identified as a funding source in any of the CVs.

This Reviewer concludes there were no disclosable interests.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry, Manufacturing, and Controls (CMC) review was performed by Wei Guo, PhD with input from other members of the Division of Therapeutic Proteins (DTP) including Emanuela Lacana PhD, Barry Cherney PhD, and Amy Rosenberg, MD. According to DTP, the active pharmaceutical ingredient (API) of the TbMP is pancrelipase, and the API of the CMP is

10 Center for Drug Evaluation and Research: Guidance for IndustryE6 Good Clinical Practice: Consolidated Guidance. April 1996. http://www.fda.gov/cder/guidance/959fnl.pdf

also pancrelipase but manufactured using different source materials and under different processes. One excipient in the CMP, dibutyl phthalate, is not used in the TbMP due to concerns of potential toxicity over long term exposure. A second excipient in the CMP, mineral oil, is not used in the TbMP because of the theoretical risk that long-term exposure might interfere with absorption of fat soluble vitamins. Removal of these excipients are thought to enhance the safety of the TbMP.

Dr. Guo's review did not identify issues that would preclude approval and per telephone conversation with Dr. Guo on 4-February-2009, the following two items have been resolved:

- Provision data supporting duration of allowed temperature excursions from 15 to 30^{o} C.
- Provision of in-use stability data once Creon is removed from foil-wrap packaging.

4.2 Clinical Microbiology

The Clinical Microbiology review was performed by Ennan Guan, MD, PhD. Dr. Guan did not identify any issues that would preclude approval. Notable issues in Dr Guan's review are summarized below:

> The microbiology review requested designation of specifications for infectivity assays for PCV 1 and PCV2, and Reo genomic equivalents, as well as an assessment of daily genomic viral load with projected daily dose of drug.
>
> Specifications for non-enveloped viruses were not appropriate. The detectable infectivity should be "undetectable" rather than by the proposed lower limits of detection (see Dr. Guan's final review).
>
> The review requested further clarification and description of a risk mitigation plan for control of adventitious agents, emerging disease surveillance, and description of cross contamination prevention procedures.

Outstanding viral issues do not preclude approval and will be addressed in PMRs/PMCs described in sections 1.3 and 1.4 of this review.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology-Toxicology review (David Joseph, PhD 18-November-2008) reveals no issues that preclude approval.

Notable comments from Dr. Joseph's review are limited to a recommendation for "Pregnancy Category C. Animal reproduction studies have not been conducted with pancrelipase. It is also not known whether pancrelipase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity." Though Creon and other porcine derived pancrelipases are not

thought to be absorbed from the gut in clinically meaningful amounts, this Reviewer agrees with Dr. Joseph's recommendation.

4.4 Clinical Pharmacology

The Clinical Pharmacology review was performed by Tien-Mien Chen PhD (10-November-2008). Dr. Chen found no issues that would preclude approval. The comments in the following sections were discussed with Dr. Chen for inclusion in this review and he agrees with this summary of his assessments.

4.4.1 Mechanism of Action

Endogenous lipase, protease, and amylase proteolytically cleave complex fats, proteins, and carbohydrates to glycerol and fatty acids, peptides and amino acids, and dextrins, respectively. These cleavage products are smaller and more readily absorbed than the parent compounds. Porcine derived lipase, protease and amylase have the same mechanism of action.

The candidate product is enteric-coated to help resist gastric destruction or inactivation.

4.4.2 Pharmacodynamics

Pharmacodynamic studies were not performed with the TbMP. The active ingredients of PEPs (lipase, amylase, and protease) act locally in the gastrointestinal (GI) tract and are not absorbed; therefore, dynamic studies are not applicable.

4.4.3 Pharmacokinetics

The active ingredients of PEPS (lipase, amylase, and protease) act locally in the gastrointestinal (GI) tract and are not absorbed; therefore, pharmacokinetic studies are not applicable. Dr. Chen's review concludes "the release of lipase activity was well within the specification limit of NLT (b) (4)% (Q) after 30 and 60 minutes. There was no major difference in the 30 to 60 minute incubation periods. However, a very slight decrease from 30 to 60 minutes was observed in Carrots (Gerber Company), where the pH values measured was 5.1."

Dr Chen's review concludes the alternate method of sprinkling pellets on food should not affect the quality of the product and "complies with the dosing of whole capsules with respect to gastric resistance and release of lipase activity".

These findings suggest that opened capsules may be used to administer doses in young children and other patients who may not be able to swallow intact capsules.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The CR contains information from 60 clinical studies of TbMP, CMP and Other PEPs.

Since the previously reviewed bridging study (S248.2.003) could not be relied upon to establish comparability of *in vivo* gut-lipase activity between TbMP to CMP (see Approvable Letter, August 2007), safety and efficacy assessments in this review will focus on clinical results from the single randomized, double-blind, placebo-controlled study of the TbMP [S245.3.126, the Pivotal Study].

However, since it has been determined that multiple/all porcine-derived PEP NDAs may rely at least partly on published literature, this Reviewer performed a brief review of the updated Integrated Summary of Safety (ISS) and post-market CMP information submitted in the NDA in order to assess deaths potentially associated with administration of any PEP (TbMP, CMP, and other PEPs), as well as AEs from 15 randomized, blinded, placebo-controlled studies of CMP. Studies and reports discussed this review are summarized in Table 2.

Table 2: Studies and Reports Discussed in this Review

Items Discussed in the Body of this Review				
Study	**Description**			**Location in Clinical Review**
S245.3.126 Pivotal Study	Two-week Randomized, Double-Blind, Placebo-Controlled, Cross-Over Trial in Patients with Cystic Fibrosis, ≥12 years old; N=32, To-be-Marketed Product (TbMP)			Sections 5, 6, and 7
Integrated Safety Summary Update/Post Market Safety Summary; TbMP, Currently-marketed Product (CMP) and other PEPs				Section 7.1 and 7.3
Randomized Double-Blind Placebo-Controlled Studies of CMP				
Study	**Disease**[1]	**Age in years (y)**	**N:n** [2] **and Duration in Days**	**Location in Clinical Review**
223.2.01	CP	31 to 75	27:13 patients x 14 days	Appendix 9.5
K245.5.005	CP	39 to 69	40:17 patients x 14 days	
S245.3.107	CP	44 to 66	4:4 patients x 7 days	
S245.3.115	CP/PY	26 to 83	94:23 patients x 7 days CP 40 patients x 7 days PY	
S245.3.112	DM	47 to 61	6:3 patients x 7 days	
S245.3.113	DM	36 to 73	23:13 patients x 7 days	
S245.3.110	DM	24 to 64	80:39 patients x 112 days	
S245.3.116	HIV	29 to 53	10:6 patients x 28 days	
S245.3.119[3]	HIV	18 to 57	38:38 patients x 14 days	
S248.4.001	AP	24 to 81	56:27 patients x 28 days (26 to 30 days)	
S248.4.002	AP	32 to 78	21:10 patients x 84 days	
S245.3.102	GY	47 to 79	11:3 patients x 2 weeks	
S223.3.101	CF	12 to 18	47:18 patients x 7 days	
S223.3.102	CF	18 to 53	50:18 patients x 6 days	
Randomized Single-Blind Placebo-Controlled Study of CMP				
Kreo 629	CF	6 to 15	11:11 patients x 12 days	

[1]CF=Cystic Fibrosis, CP=Chronic Pancreatitis, PY=Pancreatectomy, DM=Diabetes Mellitus, HIV=Human Immune Deficiency Virus, AP=Acute Pancreatitis. and GY=gastrectomy
[2] N:n=Randomized patients: Patients receiving Placebo-Controlled CMP (excluding open-label wash-out or run-in periods)
[3]Discussed in Appendix 9.6.2

Except for Study S245.3.119, these 15 studies were completed and incorporated into the Complete Response received by FDA in 2006 and have undergone prior substantive review for safety and no new clinical information from these studies was submitted (Ethan D. Hausman MD, August 16, 2007).

Additional clinical information from 9 other studies was submitted which did not materially alter safety or efficacy assessments, since the studies were all performed with the CMP. These studies are briefly summarized in Table 3 below and in Appendix 9.6 of this review.

Table 3: Other Newly Submitted Studies Summarized in Appendix 9.6 and 9.7

Completed Studies				
Study	**Disease**[1]	**Age in years (y)**	**Study Description; N:n**[2]	**Location in Clinical Review**
S245.2.002	CF	6 to 16	3-day placebo run-in, 53-week uncontrolled study of currently-marketed-product (CMP); 5:5	Appendix 9.6
S245.3.117	CF	12 to 21	Open-label, uncontrolled study of CMP; 3:3	
K245.5.703	CP and PY	22 to 73	5-day placebo run-in; 5-week open-label dose exploration study CMP:CMP; 26:24	
S245.3.104	CP, GY, PY	29 to 75	5-day placebo run-in, 4-week open-label uncontrolled study of CMP, 85:83	
S245.3.103	*Open-label uncontrolled Extension Study of K245.5.703 and S245.3.104; 63:63*			
Incomplete Studies; Study Reports and Safety Data Unavailable				
S245.4.007	GY	Not Stated	6 month, randomized, double-blind, placebo-controlled study, CMP; 41:20,	Appendix 9.7
S245.3.122	CP, PY	Not Stated	One week randomized, double-blind, treatment control study; Control=Other PEP. Followed by one year open label treatment; 24:Unkown	
S245.2.123	*Extension*		*N=Unknown*	
S245.3.124	CP, PY	Not Stated	6-month randomized, double-blind, placebo-controlled study. CMP:other PEP. Age range not stated; 23:Unknown	

[1]CF=Cystic Fibrosis, CP=Chronic Pancreatitis, PY=Pancreatectomy, and GY=gastrectomy
[2] N:n=Randomized patients: Patients receiving Placebo Controlled CMP (excluding open label wash-out or run-in periods)

The remainder of the clinical information in the CR is not used to establish or supplement the safety of the TbMP for the following reasons:

- Lack of bridging of TbMP to the products used in those other studies (non-TbMP/non-CMP products).

- Inconsistent methods including data quality/integrity issues with several of the studies, inconsistent dose, differing indications (EPI vs. malnutrition not otherwise specified), and different diseases studied (see Clinical Review, Ethan D. Hausman, August 16, 2007). For these same reasons, this Reviewer concludes that pooling of safety data from these studies of non-TbMP/non-CMP studies is neither statistically nor epidemiologically appropriate.

5.2 Review Strategy

A determination efficacy of the TbMP primarily based on clinical data from the Pivotal Study which is the only adequate and well-controlled study of the TbMP. Literature describing the risk/benefit balance of PEP is summarized in section 2.6 of this review.

Safety, and the strategy for the safety review, is discussed in section 7 of this review.

5.3 Discussion of Individual Studies

5.3.1 Methods

Section 5.3.1 describes the design, study population, treatment, objectives and outcome measures, inclusion and exclusion criteria, concomitant medications, pertinent protocol amendments, and statistical plan. Subsequent sections of 5.3 include outcome descriptions including, but not limited to, primary and secondary efficacy outcomes.

Determination of efficacy is based on the primary endpoint, mean difference (change) in CFA (CFA during Creon treatment minus CFA during Placebo treatment). Secondary efficacy endpoints including mean change in CNA (Creon minus placebo), change in stool pattern, and patient/investigator symptom scores were not used to establish efficacy. Summary findings from secondary efficacy endpoints are discussed where noted.

5.3.1.1 Design, Population, Treatment

Title: "A double-blind, randomized, multi-center, placebo-controlled, cross-over study to assess the efficacy and safety of Pancrelipase Delayed Release 24000 Unit Capsule in subjects with pancreatic exocrine insufficiency due to cystic fibrosis." (S245.3.126, Pivotal Study)

The Pivotal Study was a 3-week, multi-center, randomized, double-blind, Placebo-controlled, 2-arm, cross-over (CO) study of the to-be-marketed formulation; Creon 24,000 lipase unit (Lu) capsules (hereafter, Creon) in patients with CF ages 12 years and older. Patients must have been on stable doses of any other PEP treatment (prior PEP) for at least 3 months to qualify for enrollment. Diet was determined for each patient based on his or her caloric requirement, with 40% of the calories from fat, with a minimum fat intake of $\geq$100 gram fat/day. Creon dose was 4,000 Lu/gram of dietary fat/meal; however, patients who were receiving >4,000 Lu/gram fat/meal prior to the Pivotal Study were given the same Lu/gram fat dose of Creon during the Pivotal Study. Patients were randomized 1:1 to either of the CO sequence: Creon→Placebo, or Placebo→Creon. Each CO treatment period lasted 5 to 7 days. Seventy-two hour stool collections for CFA analyses commenced on the evening of Day 2 of each CO period.

Treatment effect for each patient was defined as mean CFA obtained during the Creon treatment period (Creon CFA) minus mean CFA obtained during the Placebo treatment period (Placebo CFA). Patients were their own controls. Thirty-four patients were screened, 32 patients received at least one dose of Placebo or Creon, and 31 patients completed all study procedures.

The CO periods were separated by a three to 14 day washout period (WO), during which time treatment with Creon or Placebo was discontinued and patients resumed their prior PEP at their pre-study PEP therapy at their pre-study dose, and an *ad lib* diet.

Table 4 provides a schematic of the study procedures. On completion of Screening at Visit 1 (V1), patients continued prior PEP treatment until V2, 3 to 14 days later. At V2, Day 1 of CO1, patients were hospitalized and randomized to Creon→Placebo or Placebo→Creon indicating

treatment for CO1→CO2, respectively. Randomized study drug treatment began on Day 1 of each CO period. Ingestion of the planned diet began on Day 1 and lasted for 5 to 7 days during each CO period. Doses were divided evenly between 3 meals and 2 to 3 snacks per day. Snack doses were ½ meal doses.

Stool collections for 72-hour CFA analyses began on the evening of Day 2 of each CO period.

Safety follow-up was performed within 7 days after V5.

Table 4: Pivotal Study Design

Screening Period	**Cross-Over Period 1 (CO-1); 7 Days Inpatient**		**Wash-out**	**Cross-Over Period 2 (CO-2); 7 Days Inpatient**		**Follow-Up**
Visit 1	Visit 2 (Day 1)	Visit 3 (Day 6 or 7)	3 to 14 days	Visit 4 (Day 1)	Visit 5 (Day 6 or 7)	One week after Visit 5
Screening procedures; Continue Prior PEP	Day 1 of DB treatment; Creon or placebo	Complete 1st 72 hour CFA collection	Prior PEP; Regular diet	Day 1 of DB treatment; placebo or Creon	Complete 2nd 72 hour CFA collection	Safety Follow-Up
	Study Diet Days 1 to 7. 72 hr CFA start on the evening of Day 2.			Study Diet Days 1 to 7. 72 hr CFA start on the evening of Day 2.		

Source: After Table 2, page 23 of the Clinical Study Report, NDA Volume 3, page 1,142.

Stool collections for CFA were performed as described: The first of two stool dye markers was ingested on the evening of Day 2 of CO1. Passage of the first stool with the corresponding dye marked the beginning of collection. A second stool dye marker was ingested on the evening of Day 5 of CO1. The first stool with the corresponding dye marked the end of the 72-hour stool collection (Day 6 or 7). Stool CFA procedures for CO2 were identical. Safety follow-up was performed within seven days after completion of the second CFA collection (V5).

5.3.1.2 Objectives and Outcome Measures

The primary efficacy objective was to demonstrate a mean change in CFA >14% [Creon minus placebo]. CFA was an agreed upon efficacy measure and determination of efficacy is based solely on this analysis.

- FDA considers efficacy to be demonstrated by a ≥30% difference in CFA in patients with severe EPI such as patients with Baseline CFA ≤40%. Therefore, this Reviewer will make a determination of efficacy based on demonstration of a ≥30% difference between Creon and Placebo treatment groups.

Secondary efficacy objectives were exploratory and included differences in coefficient of nitrogen absorption (CNA) [Creon minus Placebo], and changes in stool fat, stool weight, and clinical symptoms (stool frequency, stool consistency, abdominal pain, flatulence). Determination of efficacy is not based on these exploratory efficacy endpoints. Selected findings will be presented where noted.

Safety objectives were to describe short-term safety findings including differences in adverse events (AEs), vital signs, body weight, physical examination findings, and clinical laboratory values between Creon and placebo treatment.

5.3.1.3 Visits and Procedures

Screening procedures included collection of informed consent, demographic data, medical history including usual pre-study diet and prior PEP and dose (in Lu/kg/day), calculation of the diet requirements for the study, and assessment of inclusion/exclusion criteria. In addition to CFA and CNA assessments, clinical laboratory assessments included pregnancy tests in age and gender appropriate patients, complete blood counts, clinical biochemistry tests, and urinalyses (Tables 5 and 6).

Table 5: Study Assessments; Screening, Crossover (CO), and Follow-Up (F/U) Visits

Study Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Safety F/U**
Study Day	Day -14 to -1	CO1 Day 1	CO1 Day 6 or 7	CO2 Day 1	CO2 Day 6 or 7	
Screening Procedures	X					
Physical examination, height	X		X		X	
Weight, vital signs	X					
Laboratory Tests	X		X	X	X	
Clinical Global Impression	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X
Symptom History	X			X		
Treatment and Assessments Within CO Periods	**See Table 6**					

Source: Table 3, page 30 of the Clinical Study Report, NDA Volume 3 pate 1,149.

Table 6: Study Assessments During Crossover Periods

Study Day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 or 7
Hospital Entry; Start Study Diet	X					
Dose Administered	X	X	X	X	X	
Compliance Assessed	X	X	X	X	X	
Stool Dye #1 Ingested; evening		X				
Record Diet Begins with Day 2 dye ingestion		X	X	X	X	
Stool Collection		X	X	X	X	X
Symptom History	X	X	X	X	X	
Weight	X	X	X	X	X	X
Stool Dye #2 Ingested; evening					X	
End Hospitalization						X

Source: Table 4, page 30 of the Clinical Study Report, NDA Volume 3 pate 1,149.

5.3.1.4 Eligibility/Inclusion and Exclusion Criteria

Notable inclusion criteria are:

- Diagnosis of CF by iontophoresis (sweat test) or genetic testing.
- Evidence of EPI documented by a CFA <70% without PEP supplement or a fecal elastase <50 ug/gram stool within one year of Screening.
- Ages 12 years and older.
- Treatment with prior PEPs (not TbMP) at stable doses for ≥ 3months prior to Screening.
- No more than a 5% loss in body weight within the three months prior to enrollment.

Notable exclusion criteria are:

- Patients younger than 18 years old could not have a body mass index <10%.
- Presence of acute or chronic illness at Screening thought to potentially interfere with safety or efficacy assessments; specifically:
    - Pancreatitis or distal ileal obstruction syndrome (DIOS) within six months prior to enrollment.
    - Gastrointestinal malignancy within the preceding five years
    - History of fibrosing colonopathy or inflammatory bowel disease
    - Small bowel surgery other than minor resection due to meconium ileus without resulting in malabsorption syndrome

5.3.1.5 Study Medication Dose Selection

Dose was 4,000 Lu/gram of dietary fat/day, based the maximum dose in Lu/gram of fat ingested/day recommended by CFF Guidelines.[2, 3, 5] The CFF Guidelines state this diet should

consist of at least 100 grams of fat with 40% of calories to be derived from fat.[2,3] Doses were to be administered over a 3 meal and 2 to 3 snack schedule. Snack doses were ½ the meal dose.

Another regimen outlined in the CFF Guidelines delineates dose in Lu/kg/meal. Doses above 2,500 Lu/kg/meal should only be considered after an evaluation rules out treatable reasons for therapeutic failures, such as undocumented fat intake or lactose intolerance. Clinical improvement and increased CFA should be documented with doses higher than 2,500 Lu/kg/meal [10,000 Lu/kg/day divided across 3 meals plus 2 to 3 snacks]. Doses higher than 6,000 Lu/kg/meal should not be used because the risk of fibrosing colonopathy outweighs potential benefit.

A sample dose calculation is shown for illustrative purposes. In a 40 kg patient consuming 100 gram/fat/day, 4,000 Lu/gram fat/day is equivalent 2,500 Lu/kg/meal [10,000 Lu/kg/day], which is the maximum recommended dose in the CFF Guidelines. [2, 3, 5] A summary of the CF PEP dosing guidelines is found in section 7.6.4 of this review.

Discussion: One study assessed relative risk based on 29 CF patients with fibrosing colonopathy matched approximately 1 to 4 with age, dose, and duration of treatment matched controls. Patients treated with PEP doses less than 24,000 Lu/kg/day (6,000 Lu/kg/meal) were assigned relative risk of 1 (RR 1). Patients treated with does from 24,001 to 50,000 Lu/kg/day had a RR of 10.9 (95% C.I., 1.6 to 71.8), and patients treated with doses above 50,000 Lu/kg/day had a RR of 199.5 (95% C.I., 9.9 to 4,026). In summary, while no lipase dose is without risk, relative risk of FC increases with doses above 24,000 Lu/kg/day (6,000 Lu/kg/meal).[1]

5.3.1.6 Prior, Concomitant, and Prohibited Medications

All patients must have been on prior PEP treatment (not TbMP) at a stable (not defined) dose for at least three months prior to enrollment. Ingestion of PEPs other than Creon was not allowed during CO1 and CO2.

Medications affecting duodenal pH (for example, H2-receptor antagonists and antacids), gastric emptying (for example, metoclopramide or erythromycin), or bile secretion (such as bile acids or cholecystokinin antagonists) were allowed if:

- The medication was commercially available and prescribed according to recommended dose.
- The medication was taken for ≥4 weeks before start of the study at the prescribed dose, and the dose could not change during the course of the study.

Prohibited medications during CO1 and CO2 included the following: nutritional supplements containing medium-chain triglycerides, narcotic analgesics, antidiarrheals (added by Amendment 2), antispasmodics (added by Amendment 2), laxatives, and immunosuppressive drugs (excluding steroids).

A list of all prescription and over the counter medications/therapies taken within thirty days of Screening through final follow-up seven days after the end of CO2 were to be recorded on case report forms (CRFs).

5.3.1.7 Statistical Plan

The study was designed to demonstrate a >14% difference in CFA between Creon and Placebo with an estimated and standard deviation (SD) of 20%. The Applicant calculated that a sample size of 24 should have 90% power to detect an effect size of 0.7 using a paired t-test with a 0.05 two-sided level of significance. The Applicant estimated that 24 patients would need to complete the study. To allow for patient drop-outs, 26 patients were to be enrolled. Analyses were to be performed using ANOVA models with treatment, sequence, and period as fixed effects and patient within-sequence as a random effect.

The protocol specified that efficacy analyses would be performed on all patients receiving $\geq$1 dose of Creon or Placebo who also had CFA analyses during CO1 and CO2. This population is referred to as the Full Analysis Population (FAP).

5.3.1.8 Control, Blinding, and Randomization

Control was established by use of placebo capsules that were designed to have similar appearance, smell, and taste to Creon.

Randomization was performed at the start of CO1. Patients were randomized using a blinded centralized telephone activated voice response system. The randomization scheme was developed and implemented by a division of the Applicant; the Global Clinical Supplies Office of Solvay Pharmaceuticals BV, Weesp, Netherlands. The blind could be broken early in the event of a clinical emergency that any site investigator thought necessitated knowledge of true treatment. Any instance of unblinding was to be documented along with the reason and the name of the investigator and site requesting unblinding; this did not occur.

5.3.1.9 Protocol Amendments

The original protocol was dated 25-July-2007. Two protocol Amendments were received and are summarized in section 5.8 of the Study Report. The two Amendments are summarized below.

Protocol Amendment 1, dated 10-October-2007 implemented the following notable changes in addition to miscellaneous administrative changes:

- Removed that the nutritional service was to provide the food in order to allow flexibility in the source of the food for the subjects' diet.
    - A review of daily fat intake was performed. Adequate daily fat intake was recorded from day 2 through 5 of each CO period (see section 5.3.3.2 of this document). Therefore, this change should not affect efficacy assessments.

Protocol Amendment 2, dated 18-December-2007, implemented the following notable changes in addition to miscellaneous administrative changes:

- Established minimum fat intake and clarified/mandated similar diet in CO1 and CO2, and clarified the method for quantifying dietary intake.

- Permitted small intestine resection such as appendectomy.

- Added antidiarrheals and antispasmodics to the prohibited medications because these agents may affect secondary efficacy parameters including: abdominal symptoms, intestinal motility, and stool characteristics.

- Eliminated the need for fasting prior to blood draws.

    - This Reviewer believes the above changes to the study plan should not affect assessments of CFA. Blood glucose, cholesterol and lipid panels might be affected by not requiring fasting phlebotomy. Other clinical laboratory tests should not be meaningfully affected.

5.3.2 Demographics

A review of the demographic data was performed to assess balance in baseline characteristics of the two treatment sequences.

Thirty four patients were screened, and 32 patients received >1 dose of placebo or Creon (ITT=32). Thirty one patients completed all primary efficacy assessments (Full Analysis Population; FAP=31). Mean age was 22.5 (SD 7.1) years; median 22 years and range 12 to 43 years. Mean and median ages in the two treatment arms were similar. Median age in females was 18 years; range 13 to 38 years. Median age in males was 23.5 years; range 12 to 43 years.

The overall gender distribution was 66% male and 34% female. The male to female ratio was higher in the Placebo→Creon group (12:4) than in the Creon→Placebo group (9:7). This finding is not expected in an autosomal recessive trait such as CF and this imbalance is likely attributable to the small study size. Gender effects for severity of EPI in CF are not described in the literature and this imbalance is likely not clinically meaningful. Enrollment was 100% Caucasian and analyses by race/ethnicity could not be performed. Placebo period CFA is shown as an approximation of Baseline (non-treatment) severity; 31% of patients had placebo period CFA $\leq$40% and 69% of patients had placebo period CFA >40%; Table 7.

Table 7: Demographics

Trait	Statistic	Creon→ Placebo	Placebo →Creon	Total
Age (years)	N	16	16	32
	Mean (SD)	22.8 (6.5)	22.2 (7.8)	22.5 (7.1)
	Median	22.5	21.5	22.0
	Minimum/Maximum	12/38	22/43	12/43
Age Strata				
12 to 18 y	N (%)	5 (31)	6 (38)	11 (34)
>18 y		11 (69)	10 (62)	21 (66)
Gender				
Male	N (%)	9 (56)	12 (75)	21 (66)
Female	N (%)	7 (44)	4 (25)	11 (34)
Race				
Caucasian	N (%)	16 (100)	16 (100)	32 (100)
[1]Placebo CFA				
≤40%	N (%)	7 (44) [2]	3 (19)	10 (31)
>40%		9 (56)	13 (81)	22 (69)

Source: After Table 7, page 50 of the Clinical Study Report, NDA Volume 3, page 1,169, and this Reviewer's analysis for Placebo CFA ≤ or > 40%,
[1]Assessment rather than demographic characteristic. Used as a proxy for Non-Treatment Baseline
[2] One patient was withdrawn after the first cross-over period.

Severity of EPI in CF is known to be generally related to specific pathologic alleles (for example, delta-F508 mutation). While allele frequencies vary by race, there is no evidence demonstrating an effect of race on allele expression. Therefore, and since patients served as their own controls, this author believes the racial demographic imbalance should not affect efficacy assessments.

There were no non-US sites.

5.3.3 Patient Disposition

Thirty two randomized patients (100%) received ≥1 doses and 31 (97%) patients received ≥1 dose and completed all study procedures.

- Patient 0016-00001, a 17 year old male in the Placebo→Creon group, was removed from study during CO1 due to ingestion of dye capsule rather than randomized treatment. This patient was re-randomized as Patient 3 from Center 16 (ID: 0016-0003).

- Patient 0031-00002 was withdrawn at the end of CO1 (after Creon treatment) for violation of entry criteria [weight loss >5% for the 3 month period preceding enrollment].

- As noted in section 3.2 of this document, the Applicant reports that data from both patients as site 23 are not reliable. Since data from these two patients were able to be isolated and since review of the dataset and study report revealed no other notable data quality issues, the Statistical and Clinical reviewers concluded that efficacy assessments should be performed with and without data from these two patients.

5.3.3.1 Diet

Since dose was based on dietary fat intake this Reviewer assessed dietary fat intake. Dietary fat was to be recorded from the evening of Day 2; however, in 25 patients, this data was reported from the start of Day 2. Therefore, this Reviewer concludes that inclusion of day 2 fat data in mean daily fat assessments is unreliable. Therefore, mean daily fat is calculated from Days 3 to 5 data. This is followed by a presentation of each day's mean fat intake (Day 2 through 4).

Mean dietary fat (CO Days 3 through 5) was lower during Creon- than placebo-treatment; 160 grams and 164 grams, respectively. The magnitude of this difference was similar in both treatment sequences; Table 8.

Table 8: Grams Dietary Fat/Day; Mean (SD) Day 3 through 5

Treatment Sequence	**Creon N=32**	**Placebo N=31**
Overall	160 (49)	164 (55)
Creon → Placebo	167 (47)	171 (55)
Placebo → Creon	153 (50)	160 (56)

In both treatment sequences, documented grams of fat ingested were lower on Day 2 than Days 3, 4 and 5; 93 to 98 grams of fat on Day 2 compared to 147 to 174 grams for fat on Days 3, 4, and 5; Table 9.

Table 9: Gram Fat/Day; mean (SD)

Creon → Placebo	**Day**	**Creon (CO1) N=16**	**Placebo (CO2) N=15**
	2	93 (66)	98 (62)
	3	169 (56)	173 (57)
	4	166 (41)	167 (42)
	5	165 (47)	174 (63)
Placebo → Creon	**Day**	**Creon (CO2) N=16**	**Placebo (CO1) N=16**
	2	98 (74)	94 (75)
	3	158 (58)	162 (66)
	4	147 (41)	157 (49)
	5	156 (53)	160 (55)

Since the protocol specified that dietary assessments were to begin at the end of CO Day 2, this Reviewer concludes that a systematic protocol deviation did not occur at site 25 and since accurate diet information was recorded for Days 3 through 5, efficacy assessments should not be affected.

5.3.4 Analysis of Primary Endpoint

5.3.4.1 Discussion of Primary Efficacy Endpoint

FDA has previously established that CFA is an appropriate efficacy marker for PEP development plans given the establishment of CFA as a valid clinical endpoint correlating with improved pulmonary function and long term survival.[2, 4, 5, 8] The CFA test is performed by providing patients with pre-defined amounts of dietary fat, measuring the amount of stool fat excreted over 72 hours and reporting the percent difference:

$$\frac{[(\text{Dietary Fat} - \text{Stool Fat})]}{\text{Dietary Fat}} \times 100$$

Healthy infants less than 6 months old have CFA >85% and healthy adults have CFAs >95% (i.e., the body has the ability to absorb > 85 to 95% of the ingested fat in these ages groups), and severely affected individuals have lowest CFA values, for example CFA <40%. Treatment with exogenous PEPs increases CFA in affected individuals. Common goals of therapy are to attain a treatment CFA >80 to 85% and increases ≥30% are commonly reported as being clinically significant in severely affected patients such as those with non-treatment CFA ≤40%.[11]

Discussion: CNA is not used to establish efficacy since clinical data is not available establishing a correlation with recognized clinical benefits; for example, improved growth and pulmonary function or decreased mortality.

5.3.4.2 Results

The study was designed so that CFA values from Creon treatment in CO1 and CO2 were combined, and CFA values from placebo treatment in CO1 and CO2 were combined. Assessments were performed on the FAP (N=31) and the modified FAP (N=29) that excluded two patients with data quality issues.

For the FAP, mean CFA during Creon treatment was 89% (SD 7), mean CFA during placebo treatment was 50% (SD 18), and the mean difference in CFA was 39% (95% CI 32 to 46); p <0.001. For the modified FAP, mean CFA during Creon treatment was 89% (SD 6), mean CFA during placebo treatment was 49% (SD 18), and the mean difference in CFA was 41% (95% CI 34 to 47); p <0.001. This Reviewer concludes these findings are clinically meaningful, statistically significant, and support efficacy; Table 10.

11 Astra-Zeneca. First Principles in Gastroenterology, Web Edition, Chapter 7 Malabsorption. September. 2008

Table 10: Change in CFA (%) for Full Analysis and Modified Full Analysis Populations

	Creon	Placebo	Creon minus Placebo
Full Analysis Population			
n	31	31	
Sample Mean (s.d.)	89 (7)	50 (18)	
Adjusted Mean (s.e.)	89 (2)	50 (2)	
Adjusted Mean Treatment Difference vs. Placebo (95% C.I.)			39 (32, 46)
p-value for Adjusted Mean Treatment Difference			<0.001
Modified Full Analysis Population			
n	29	29	
Sample Mean (s.d.)	89 (6)	49 (18)	
Adjusted Mean (s.e.)	89 (2)	49 (2)	
Adjusted Mean Treatment Difference vs. Placebo (95% C.I.)			41 (34, 47)
p-value for Adjusted Mean Treatment Difference			<0.001

From Draft Statistical Review, rounded to whole integers.
Source: Table 9 on page 54 and Table 3.1.1 on page 113 of Study S245.3.126 report. Full analysis population 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. Modified full analysis population adjusted mean estimates based on the Statistical reviewer's analysis using a similar ANOVA model and without two subjects from Center 23.

5.3.4.3 Exploratory Analysis by Placebo Period CFA

Patients with lower non-treatment or Placebo CFA are expected to have a greater capacity to respond to PEP supplementation. Therefore, a sensitivity analysis of change in CFA by Placebo CFA [≤ or > 40%] was performed.

In the FAP, patients with Placebo CFA ≤40% had a mean CFA during Placebo treatment of 30% (SD 6) and a mean increase in CFA during Creon treatment of 60% (SD 4). Patients with Placebo CFA >40% had a mean CFA during Placebo treatment of 58% (SD 15) and a mean increase in CFA during Creon treatment of 30% (SD 15). Mean CFA during Creon treatment for the two groups was similar (90% and 88%). Results in the modified FAP were the similar. The result is consistent with the expectation that patients with lower Placebo (no treatment) CFA have greater capacity to response to Creon treatment (Table 11).

Table 11: Sample Mean CFA by Placebo CFA

FAP (N=31)			
Placebo CFA ≤40%; n=9	**Creon**	**Placebo**	**Creon minus Placebo**
Mean (SD)	90 (6)	30 (6)	60 (4)
Median	90	30	61
Placebo CFA >40%; n=22			
Mean (SD)	88 (7)	58 (15)	30 (15)
Median	90	55	29
Modified FAP (N=29)			
Placebo CFA ≤40%; n=9	**Creon**	**Placebo**	**Creon minus Placebo**
Mean (SD)	90 (6)	30 (6)	60 (4)
Median	90	30	61
Placebo CFA >40%; n=20			
Mean (SD)	89 (7)	57 (15)	32 (15)
Median	91	55	30

In general, patients with lower CFA during Placebo treatment (≤40%) tended to have the greatest increase with Creon treatment (≥60%). This is illustrated in Table 12 which displays CFA for each patient (Placebo CFA, Creon CFA, and change in CFA). Patients are presented by in sequence by ascending Placebo CFA.

Table 12: CFA by Treatment for each Patient (N=31)

Treatment Period		**Creon minus Placebo**		**Treatment Period**		**Creon minus Placebo**
Placebo	**Creon**			**Placebo**	**Creon**	
23	84	61		47	92	45
23	82	59		51	78	27
23	84	61		51	81	30
29	91	62		54	93	39
30	93	63		55	96	40
32	90	59		58	88	30
32	96	64		64	87	23
38	98	60		67	93	27
40	90	50		67	82	16
41	90	49		68	95	27
41	94	53		72	93	21
42	93	51		72	97	24
43	72	29		77	84	7.3
43	80	37		83	78	-5
43	89	46		91	96	5
43	88	45				

The patients with a -5% and 5% change in CFA had a placebo period CFA >80% which suggests mild EPI. Prior review of this NDA indicates that in some instances milder disease masks response and such findings in one or two patients is not unexpected.

Table 26 in the Appendix 9.4 of this document lists each patient's CFA by treatment, change in CFA, dose in Lu/gram fat/day and Lu/kg/day, age and gender.

5.3.4.4 Exploratory Analyses by Dose

A sensitivity analysis was performed by dose in Lu/gram fat/day (≤ or > 4,000) because this is a commonly applied dose limit described in the CFF Guidelines. For the FAP, mean CFA during Creon treatment in both groups was similar (86 to 90%) and mean increase in CFA was likewise similar (37 to 40%); results in the modified FAP were similar (Table 13).

Table 13: Sample Mean CFA by Dose in Lu/Gram Fat/Day

FAP (N=31)			
≤4,000 Lu/Gram Fat/Day (N=10)	**Creon**	**Placebo**	**Creon minus Placebo**
Mean (SD)	86 (5)	48 (15)	37 (17)
Median	86	43	45
>4,000 Lu/kg/day (N=21)			
Mean (SD)	90 (7)	50 (20)	40 (20)
Median	93	43	39
Modified FAP (N=29)			
≤4,000 Lu/Gram Fat/Day (N=8)	**Creon**	**Placebo**	**Creon minus Placebo**
Mean (SD)	87 (4)	45 (12)	42 (13)
Median	88	43	45
>4,000 Lu/kg/day (N=21)	90 (7)	50 (20)	40 (20)
Mean (SD)	93	43	39
Median	72, 98	23, 91	-5, 64

A sensitivity analysis by dose in Lu/kg was also performed was also performed since this is a commonly applied dose limit described in the CFF Guidelines [10,000 Lu/kg/day or approximately 2,500 Lu/kg/meal]. For the FAP, mean CFA during Creon treatment in both groups was the same (89%) and mean increase in CFA was likewise similar (38 to 39%); results in the modified FAP were similar (Table 14).

Table 14: Sample Mean CFA by Dose in Lu/kg/day

FAP (N=31)			
≤10,000 Lu/kg/day, N=14	**Creon**	**Placebo**	**Creon minus Placebo**
Mean (SD)	89 (6)	51 (20)	38 (21)
Median	89	43	45
>10,000 Lu/kg/day, N=17			
Mean (SD)	89 (7)	49 (17)	39 (17)
Median	92	47	39
Modified FAP (N=29)			
≤10,000 Lu/kg/day, N=13	**Creon**	**Placebo**	**Creon minus Placebo**
Mean (SD)	89 (6)	49 (19)	41 (21)
Median	89	43	46
>10,000 Lu/kg/day, N=16			
Mean (SD)	89 (7)	49 (18)	40 (17)
Median	92	45	40

The mean dose in patients receiving less than 10,000 Lu/kg/day was 8380 Lu/kg/day and the mean dose in patients receiving higher than 10,000 Lu/kg/day was 12,185 Lu/kg/day. This Reviewer hypothesizes that the similar change in CFA between groups is because dosage in Lu/gram dietary fat/day in these two groups was similar (3,916 and 4,372 Lu/gram).

5.3.5 Analysis of Secondary Endpoints(s)

The secondary efficacy assessment was the difference in mean coefficient of nitrogen absorption (CNA) between Creon and Placebo treatment. The study was designed so that CNA values from Creon treatment in CO1 and CO2 were combined, and CNA values from placebo treatment in CO1 and CO2 were combined. A target increase in CNA in Creon compared to placebo patients was not pre-specified.

For the FAP, mean CNA during Creon treatment was 85% (SD 6), mean CNA during placebo treatment was 50% (SD 17), and the mean difference in CNA was 35% (95% CI 30 to 41). For the modified FAP, mean CNA during Creon treatment was 86% (SD 6), mean CNA during placebo treatment was 49% (SD 17), and the mean difference in CNA was 37% (95% CI 31 to 42). These findings are statistically significant but clinical meaning is uncertain (Table 15).

Table 15: Change in CNA (%) for Full Analysis and Modified Full Analysis Populations

	Creon	Placebo	Creon minus Placebo
Full Analysis Population			
n	31	31	
Sample Mean (s.d.)	85 (6)	50 (17)	
Adjusted Mean (s.e.)	85 (2)	50 (2)	
Adjusted Mean Treatment Difference vs. Placebo (95% C.I.)			35 (30, 41)
Modified Full Analysis Population			
n	29	29	
Sample Mean (s.d.)	86 (6)	49 (17)	
Adjusted Mean (s.e.)	86 (2)	49 (2)	
Adjusted Mean Treatment Difference vs. Placebo (95% C.I.)			37 (31, 42)

From Draft Statistical Review, rounded to whole integers.
Source: Table 10 on page 55 and Table 3.4.1 on page 121 of Study S245.3.126 report. Full analysis population 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. Modified full analysis population adjusted mean estimates based on the Statistical reviewer's analysis using a similar ANOVA model and without two subjects from Center 23.

These finding suggest that a positive nitrogen balance is achieved in patients with EPI treated with PEPs. Improved nitrogen homeostasis may be a desirable outcome in chronically malnourished patients; however, the long-term clinical significance of this finding is undetermined since clinical data is not available establishing a correlation of CAN with recognized clinical benefits such as improved growth and pulmonary function or decreased mortality.

Discussion of additional efficacy endpoints is limited to changes in stool weight, frequency, and Global Impression (symptoms scores) which are summarized below. Change in stool fat content and stool nitrogen content are incorporated into CFA and CNA analyses and are not further discussed. These additional assessments have not been recognized by the Division as clinical endpoints for labeling purposes and these data are summarized for illustrative purposes only.

In the FAP, mean stool weight with Creon treatment (630 grams) was 953 grams/day less than during placebo treatment (1583 grams). In the modified FAP, mean stool weight during Creon

treatment (589 grams) was 980 grams/day less than during placebo treatment (1569 grams). These findings support effectiveness in decreasing stool weight, Table 16.

Table 16: Change in Stool Weight and Frequency

FAP (N=31)			
Stool Weight (gram)	**Creon**	**Placebo**	**Creon minus Placebo**
Mean (SD)	630 (307)	1583 (665)	-952 (528)
Median	569	1534	-888
Stool Frequency			
Mean (SD)	1.75 (0.81)	2.88 (1.18)	-1.10 (0.84)
Median	1.67	2.67	-1.17
Modified FAP (N=29)			
Stool Weight (gram)	**Creon**	**Placebo**	**Creon minus Placebo**
Mean (SD)	589 (271)	1569 (684)	-980 (534)
Median	567	1493	-920
Stool Frequency			
Mean (SD)	1.73 (0.84)	2.91 (1.21	-1.14 (0.85)
Median	1.67	2.67	-1.17

Source: This Reviewer's analysis.

At screening, patients in both treatment sequences reported similar symptom scores (data not shown). In the FAP, more patients reported severe symptoms at the end of Placebo treatment (62% none to mild) than at the end of Creon treatment (100% none to mild). Findings in the modified FAP were similar; 59% none to mild at the end of placebo treatment compared to 100% none to mild at the end of Creon treatment; Tables 17 and 18.

Table 17: Change Patient Global Impression (symptoms), Full Analysis Population (N=31)

Symptoms; N (%)	**Creon**	**Placebo**
Start of Randomized Treatment	N=32	N=31
None	15 (47)	10 (32)
Mild	17 (53)	21 (68)
Moderate	0	0
Severe	0	0
Incapacitating	0	0
End of Randomized Treatment	N=31	N=31
None	17 (53)	8 (26)
Mild	13 (47)	9 (36)
Moderate	0	11 (36)
Severe	0	1 (3)
Incapacitating	0	0

Source: This Reviewer's analysis.

Table 18: Change Patient Global Impression (symptoms), Modified Full Analysis Population (N=29)

Symptoms; N (%)	Creon	Placebo
Start of Randomized Treatment	N=30	N=29
None	15 (50)	10 (35)
Mild	15 (50)	19 (65)
Moderate	0	0
Severe	0	0
Incapacitating	0	0
End of Randomized Treatment	N=29	N=29
None	17 (57)	8 (28)
Mild	13 (43)	9 (31)
Moderate	0	11 (38)
Severe	0	1 (3)
Incapacitating	0	0

Source: This Reviewer's analysis.

In conclusion, Creon treated patients had fewer and less severe clinical symptoms including lower stool frequency, fewer and less severe abdominal complaints, firmer stool consistency, and less flatulence. There were no clinically meaningful or statistically significant differences in Clinician's Global Impression between Creon and placebo treatment (data not shown).

5.3.6 Subpopulations

This Reviewer performed supplementary analyses of change in CFA by gender and age.

There were 21 males and 10 females in the FAP. CFA during Creon treatment in males and females was similar (88 to 89%). Females had a greater increase in CFA than males [44% (SD 18) vs. 36% (SD 19)] due to lower placebo CFA in females compared to males [45% (SD 20) vs. 52% (SD 17)]. This Reviewer notes that the difference in CFA during placebo treatment between males and females (7%) is likely not clinically meaningful and increases in CFA with Creon treatment in both groups reached clinically meaningful levels ($\geq$30%). The Reviewer concludes that clinically meaningful differences in CFA response by gender were not demonstrated. Results in the modified FAP were similar (Table 19).

Table 19: Sample Mean CFA by Gender

FAP (N=31)	Creon	Placebo	Creon minus Placebo
Males (N=21)			
Mean (SD)	88 (7)	52 (17)	36 (19)
Median	90	43	37
Females (N=10)			
Mean (SD)	89 (6)	45 (20)	44 (18)
Median	89	44	47
Modified FAP (N=29)	**Creon**	**Placebo**	**Creon minus Placebo**
Males (N=20)			
Mean (SD)	89 (7)	52 (18)	37 (19)
Median	91	43	38
Females (N=9)			
Mean (SD)	90 (6)	42 (18)	48 (25)
Median	90	40	50

Source: This Reviewer's analysis

Patients were arbitrarily dichotomized around age 18 years (i.e., 12 to <18 years or ≥18 years). In the FAP, 10 patients were 12 to <18 years old and 21 patients were ≥18 years old. CFA during Creon treatment in both groups was similar (85 to 90%), and mean change in CFA with treatment was similar (42% and 38%). The Reviewer concludes that clinically meaningful differences in CFA response by age were not demonstrated. Results in the modified FAP were similar (Table 20).

Table 20: Sample Mean CFA by Age

FAP (N=31)	Creon	Placebo	Creon minus Placebo
12 to <18 years (N=10)			
Mean (SD)	85 (7)	43 (20)	42 (19)
Median	84	43	41
≥18 years (N=21)			
Mean (SD)	90 (6)	53 (17)	38 (19)
Median	93	51	4740
Modified FAP (N=29)	**Creon**	**Placebo**	**Creon minus Placebo**
12 to <18 years (N=9)			
Mean (SD)	85 (7)	40 (17)	45 (16)
Median	84	43	46
≥18 years (N=20)			
Mean (SD)	91 (5)	53 (17)	38 (20)
Median	93	49	43

Source: This Reviewer's analysis.

Table 26 in the Appendix 9.4 of this document lists each patient's CFA by treatment, change in CFA, dose in Lu/gram fat/day and Lu/kg/day, age and gender.

5.3.7 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose in this study was per gram of fat intake. A single dose was studied (4,000 Lu per gram fat ingested per day) which was at the upper limit of current Cystic Fibrosis Foundation (CFF) guidelines.

Dose recommendations for labeling should follow current CFF guidelines.[2, 3]

5.3.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and tolerance to therapeutic effect were not assessed. Loss of therapeutic effect is rare in published literature; however, as EPI progresses patients may require increasing doses to maintain therapeutic effect.

5.3.9 Additional Efficacy Issues/Analyses

No additional efficacy analyses were performed.

5.3.10 Efficacy Summary

Efficacy determination is based on mean change (difference) in CFA [Creon minus placebo] in patients during the Pivotal Study.

For the primary efficacy endpoint, mean change in CFA, the mean difference in CFA for the FAP was 39% (95% CI 32 to 46); $p < 0.001$. For the modified FAP, the mean difference in CFA was 41% (95% CI 34 to 47); $p < 0.001$. These results are clinically meaningful and statistically significant. This Reviewer concludes that short-term efficacy of the TbMP has been demonstrated in patients with CF, ages 12 years and older.

Patients with Placebo CFA >40% had a mean increase in CFA of 30% (SD 15) with Creon treatment; patients with Placebo CFA $\leq$40% had a mean increase in CFA of 60% (SD 4) with Creon treatment. Assessments by age and gender did not reveal clinically meaningful differences; across age groups and genders, mean CFA during Creon treatment was similar (85% to 91%), and differences in mean change in CFA were driven by differences in Placebo CFA (40% to 53%). The results suggest that patients with lower Placebo (no treatment) CFA have a greater capacity to respond to Creon treatment at a fixed dose, and that age and gender did not meaningfully affect response.

For the secondary endpoint, mean change in CNA, the mean difference in CNA for the FAP was 35% (95% CI 30 to 41). For the modified FAP, the mean difference in CNA (Creon minus placebo) was 37% (95% CI 31 to 42). These results are statistically significant and of uncertain clinical meaning.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The originally submitted indication was for "treatment of maldigestion in patients with exocrine pancreatic insufficiency."

The agreed upon indication is "treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions."

Efficacy assessments are discussed in section 5 of this review.

7 Review of Safety

Safety Summary

7.1 Method

7.1.1 Strategy

Short-term safety from one randomized, double-blind, placebo-controlled (RDBPC) study of the TbMP is reviewed.

Discussion: The ISS update contains information from 59 other studies. Of these other studies, there were 28 multi-dose clinical trials of currently-marketed-product (CMP), 5 single-dose trials of CMP, 22 studies of other PEPs, and 4 incomplete studies of CMP. Except for one RDBPC study of CMP with data integrity issues, the majority of these data were analyzed during prior review cycles (see Clinical Reviews, Ethan D. Hausman, MD, August 16, 2007; Fathia Gibril, MD, December 9, 2003). A thorough review of the ISS update and post-marketing safety report revealed no new clinically noteworthy findings. Therefore, discussion of the ISS update is limited to a presentation of deaths reported in the ISS update in section 7.3.1 of this document and a brief summary of safety data from 15 controlled studies of the CMP which are summarized in Appendix section 9.5 of this document.

Of the 44 studies in the ISS that are not discussed in this review, the following issues render the data inappropriate for labeling: variations in product formulations and doses (including *ad hoc* dosing) across studies, variations in blinding and control (including none), multiple adverse event recording systems (MedDRA, WHOART, none), and lack of

established comparability or bridging of non-CMP/non-TbMP formulations used in those studies with the TbMP formulations.

7.1.2 Methods

Safety analysis of the Pivotal Study was performed by noting the type and incidence of AEs. Deaths, SAEs, and withdrawals (WDs) are reported from the time of informed consent through completion of the final safety assessments approximately 30 days after completion of the second cross-over period. Non-serious AEs are reported from time of first dose through completion of final safety assessments approximately 1 week after the last dose. Changes from Screening in physical examinations (exams), vital signs, and clinical laboratory assessments (labs) including clinical chemistry, hematology, and urinalyses that qualified as AEs were reported in the AE datasets. AE collection methods included review of staff documentation, physical exams of patients, and review of procedural test information and clinical laboratory data. The AE safety nomenclature for this study was MedDRA. Events that occurred during the washout periods were designated as having occurred in association with the preceding controlled treatment.

7.1.3 Adequacy of Data

The clinical study report and electronic datasets from the Pivotal Study were substantially complete and relevant CRFs were available for review. This Reviewer concludes that the data from the Pivotal Study were adequate for substantive safety review.

The ISS update was substantially complete and reviewable. Individual study reports and datasets for four newly integrated studies were not submitted; however, clinical data for these four studies was incorporated into the ISS datasets which were substantially complete and reviewable.

Except for deaths and SAEs, safety information from the four non-integrated studies of CMP was not available at the time of submission of the CR.

7.1.4 Pooling Data Across Studies to Estimate and Compare Incidence

The safety experience of TbMP is limited to one 2 week, adequate and well-controlled study in CF patients, 12 to 43 years old. It is not possible to pool TbMP safety data with published literature since primary source data are not available.

TbMP and CMP safety data will not be pooled due to differences in data quality issues in multiple CMP studies including inability to confirm administered dose in lipase units.

For reasons discussed in 7.1.1 of this review pooling of data from uncontrolled studies of non-TbMP/non-CMP formulations is not statistically or epidemiologically appropriate and will not be performed in this review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Mean duration of exposure was 5.1 days (SD 0.3).

7.2.1.1 Compliance

Compliance was defined as the number of patients ingesting Creon ≥90% of the prescribed dose from Day 3 through 5 of either CO period. Eighty-seven percent of patients (27 of 31) were compliant. Twelve patients (39%) received >110% of the prescribed dose (data not shown). Creon was ingested prior to meals and review of the dataset suggests higher doses in these 12 patients were due to incomplete ingestion of meals rather than over dispensing Creon.

This Reviewer performed assessments of dose by gender, age, and placebo period CFA. By each characteristic, mean dose in Lu/gram fat/day was within protocol specified goals (4,000 Lu/gram fat +/- 10%) for all sub-groups (3,927 to 4,282 Lu/gram fat/day). Mean dose in Lu/kg/day was 11,019 (SD 3,435); range from 6,338 to 22,908 Lu/kg/day (not shown). Therefore, mean dose in Lu/kg/day approached the upper limit of dosing. Mean dose in males and females similarly was close to the maximum recommended dose in Lu/kg/day. This Reviewer notes that these excursions above 10,000 Lu/kg/day may fall within the range of clinical practice but can not be used to contravene CFF dose guidelines (Table 21).

Table 21: Mean Exposure; Day 3 through 5 Doses

Population; N	Lu/Gram Fat/Day	Lu/Kg/Day
FAP (N=31)	**4,166 (766)**	**11,019 (3,435)**
Gender		
Male (N=21)	4,272 (554)	11,522 (3,631)
Female (N=10)	3,945 (1,014)	9,950 (2,546)
Age		
12 to 18 years (N=10)	3,927 (969)	11,612 (5,149)
>18 years (N=21)	4,281 (583)	10,730 (2,179)
Placebo CFA; N		
≤40% (N=9)	4,284 (445)	10,578(2,465)
>40% (N=22)	4,118 (827)	11,210 (3,699)

Source: This Reviewer's Analysis

Mean dose in relations to intended dose and CFF dose guidelines are listing in Tables 27 and 28 in Appendix 9.4 of this document.

7.2.2 Explorations for Dose Response

The Pivotal Study was a single dosage study adjusted for daily dietary fat intake which, in addition to the small study size, limited ability to perform clinically meaningful safety assessments by dose. This Reviewer performed an exploratory assessment of AEs by dose above

and below the specified dose 4,000 Lu/gram of fat per day and above and below 10,000 Lu/kg/day dose explorations. These assessments did not reveal meaningful differences in AEs dose (data not shown).

7.2.3 Special Animal and/or In Vitro Testing

No new special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

In the Pivotal Study, TbMP was administered to 32 patients, ages 12 to 43 years, with CF. Routine clinical testing included Baseline and interval medical, surgical, and medication histories; biochemical and hematological evaluations; vital sign assessments; and periodic reassessments during CO1 and CO2. Final follow-up occurred approximately one week after the conclusion of CO2, and included interval medical, surgical, and medication histories, and follow-up clinical laboratory tests for any biochemical or hematological test that was abnormal at the end of CO2.

PEPs are not systemically absorbed and TQT assessments and studies were not performed. Electrocardiograms (ECGs) and echocardiograms (ECHOs) were performed only if indicated based on symptomatic complaints referent to the cardiovascular system. In such instances findings that would be classified as AE, for example myocardial infarction, were to be reported in the AE dataset.

7.2.5 Metabolic, Clearance, and Interaction Workup

PEPs are not systemically absorbed and metabolic and clearance assessments were not part of the Creon development plan. Concomitant medications were reviewed and no notable interactions with Creon were noted (data not shown); however, drug-drug interaction studies were not incorporated into the Creon development plan.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Fibrosing colonopathy (FC) has been reported in patients taking PEPs, and is thought to be related to high daily lipase dose, especially in young children. Reports of FC in the literature have decreased since the publication of dosing guidelines in the 1990's. One case of FC was reported in the ISS update of 2006 but the name of the commercial product and the lipase dose in use at the time of FC diagnosis are not known. There were no new cases of FC were reported in the ISS safety update. Distal intestinal obstructive syndrome (DIOS) and bowel obstruction are reported in children and adults with CF. Early reports that DIOS was pathogenically related to FC are being supplanted by opinions that DIOS is closely related to meconium ileus equivalent syndrome (MIES). In MIES intermittent bowel obstruction is caused by failure to evacuate abnormally viscous intestinal contents. Notwithstanding clinical debate, no DIOS cases were reported with TbMP, but three cases were reported in the ISS update in children receiving CMP.

Hyperuricemia is associated with PEP exposure due to the high purine content in the products. The Pivotal Study report and AE and laboratory datasets, and the ISS AE dataset, clinical report, and post-marketing report were reviewed and there were no reports of hyperuricemia.

The risks for FC, DIOS and hyperuricemia are drug-class related and are to be addressed in labeling.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during the Pivotal Study.

There were 16 deaths reported in the ISS. These deaths occurred during clinical studies, within the safety follow-up, or were reported in post-marketing notifications unrelated to clinical studies. Nine deaths are newly reported and seven were reported during prior review cycles. When deaths occurred during long-term follow-up after study closure, the deaths were reported in the text of ISS update but not in the ISS dataset. No deaths were reported with the to-be-marketed product.

Of nine newly reported deaths, three occurred during clinical studies, one during placebo treatment and two during CMP treatment. Six newly reported deaths occurred after study closure and PEP formulation and dose at time of death is unknown. No deaths appeared related to treatment with CMP. All deaths appeared to be due to complications of underlying disease, such as CF or metastatic carcinoma, or unrelated causes such as trauma.

Of seven previously reported deaths, all occurred during prior to the close of the studies. Deaths were approximately equally distributed between patients receiving Other PEPs (N=4) and Placebo (N=3). Deaths appeared to be related to complications of underlying diseases or unrelated causes. No death appeared attributable to Other PEPs (Table 22).

Table 22: New and Previously Reported Deaths

Study/Patient ID Age (y)/Gender (M/F)	Disease[1]	Treatment[2]	Clinical History
Newly Reported; During Study Integrated			
S245.3.117/1001 21 y, M	CF	CMP	Cough, respiratory failure, renal failure, and shock. Death not related to CMP. Death during safety follow-up, before end of study.
Newly Reported; During Study Not Integrated (Studies Incomplete)			
S245.4.007/208 85 y, F	GY	Placebo	Metastatic cancer and pneumonia. Death not related to CMP.
S245.4.007/402 71 y, F	GY	CMP	Complications of metastatic gastric cancer, Death not related to CMP.
Newly Reported; After Close of Follow-up Period; Not Listed in AE Dataset			
S245.3.103/2102-L-01 66 y, F	PY	CMP/?	Gall bladder cancer; Respiratory failure seven months after study. Death probably not related.
S245.3.104/2032-O-04 52 y, M	PY	CMP/?	Gall bladder cancer; Death due to liver failure as complication of primary disease; six weeks after study. Death probably not related.
S245.3.103/2170-L-01 55 y, M	PY	CMP/?	History of pancreatic cancer with pancreato-duodenectomy. Death probably not related.
S245.3.104/2140-L-02 70 y, M	CP	CMP/?	Died due to trauma induced subdural hemorrhage one day after final dose. Death probably not related.
S245.2.002/1030-C-01 9 y, M	CF	CMP/?	Respiratory failure. Death probably not related to CMP.
S245.2.002/2200-C-01 10 y, F	CF	CMP/?	Respiratory failure two weeks after treatment stopped. Death probably not related.
Previously Reported; Integrated			
223.8.01/111* 12 y, M	CF	Other PEP	Respiratory tract infection. Death not related to CMP.
CREO.630/5 89 y, F	CM	Placebo	Superinfection lung, acute respiratory failure, cardiac failure. Death not related to CMP.
CREO.630/7 71 y, M	CM	Other PEP	Malnutrition, dehydration, urinary tract infection. Death not related to CMP.
CREO.630/10 90 y, F	CM	Other PEP	Cardiac Failure. Death not related to CMP.
CREO.630/11* 87 y, F	CM	Placebo	Superinfection lung, sepsis. Death not related to CMP.
CREO.630/30 86 y, F	CM	Other PEP	Aneurysm rupture. Death not related to CMP.
CREO.631/39 77 y, M	CM	Placebo	Syncope, cardiovascular failure. Death not related to CMP.

[1]CF=Cystic Fibrosis, PY=Pancreatectomy, GY=gastrectomy, CM=Chronic Malnutrition.
[2]Treatment during study and follow-up (x/x) is indicated
*Death during in-study safety follow-up.

In conclusion, all deaths appear to have been due to complications of primary disease or unrelated causes and did not appear attributable to PEP therapy (TbMP, CMP, or other PEPs).

7.3.2 Nonfatal Serious Adverse Events

Two SAEs were reported in the Pivotal Study, both in patient 0027-0001, a 12 year-old boy in the Placebo→Creon group who experienced duodenitis and gastritis first reported 16 days after final Creon dose. He weighed 32 kg. His average daily dose was 4,331 Lu/gram fat/day (22,908 Lu/kg/day or approximately 5,090 Lu/kg/meal). His pre-study dose in lipase units/kg/day was 7,339 Lu/kg/day. The CRF was reviewed and the patient recovered without sequelae. The relationship of these SAEs to the TbMP can not be determined.

7.3.3 Dropouts and/or Discontinuations

One patient withdrew from the Pivotal Study. Patient 0031-00002 was an 18 year-old female in the Creon→Placebo group who withdrew one day after CO1 ended due to weight loss >5% within three months prior to enrollment. She weighed 57 kg and her dose was 5,130 Lu/gram fat/day (11,162 Lu/kg/day). The case summary and CRF was reviewed and this Reviewer concludes the event was not serious and was not likely related to Creon.

7.3.4 Significant Adverse Events

7.3.4.1 Severe Adverse Events in the Pivotal Study

There were two severe AEs in a single patient in the Pivotal Study. A 22 year-old female randomized to Placebo→Creon experienced upper abdominal pain during Placebo treatment and dizziness during planned phlebotomy during Creon treatment. Both AEs were severe and both AEs resolved without intervention. The AEs occurred prior to first Creon exposure.

7.3.5 Submission Specific Primary Safety Concerns

Administration of high dose PEPs (>6,000 lipase units/kg/meal) has been associated with FC. The duration of exposure required to cause FC is undetermined and the association between FC and high dose PEP treatment is not absolute as demonstrated by a report of histologically confirmed FC in a neonate with meconium ileus and no prior PEP exposure.[12] A different phenomenon termed distal intestinal obstructive syndrome (DIOS) may be reported in CF patients irrespective of PEP treatment and may present in the differential diagnosis of FC. There were no cases of FC or DIOS in the Pivotal Study. The lack of identification of FC in the Pivotal Study is probably due to the following:

- Dose (10,000 to 11,500 Lu/kg/day) and duration (5 days) may not have been sufficient to cause development of FC.
- FC is a histopathologic diagnosis and routine surveillance with endoscopy with biopsy was not performed.

12 Waters BL. Cystic Fibrosis with Fibrosing Colonopathy in the Absence of Pancreatic Enzymes. Pediatric and Developmental Pathology. 1: 74–78, 1998.

This Reviewer concludes that the risk of FC with the TbMP formulation of Creon is not refuted by the safety findings of the Pivotal Study. The risk of FC and is to be addressed in labeling.

Administration of PEPs is associated with hyperuricemia and hyperuricosuria. This is due to gastrointestinal absorption of residual porcine purines not eliminated in the product process. There were no clinically meaningful differences in blood uric acid levels during Creon vs. Placebo treatment in the Pivotal Study (see section 7.4.2, Laboratory Findings). This Reviewer notes however that the Pivotal Study was not designed to refute the potential for hyperuricemia. The risk of hyperuricemia is to be addressed in labeling.

There is an additional theoretical concern for potential transmission of adventitious porcine viruses. This risk was not assessed in the Pivotal Study. This risk and risk mitigation strategies were the focus of a meeting of the Antiviral Drugs Advisory Committee on 2-December-2008; see the CMC review for further discussion.

The reader is referred to the final REMS plan, MedGuide, and PMCs and PMRs in sections 1.3 and 1.4 of this review for a full description of activities intended to address FC and viral risk.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events during Creon treatment were similar in type to AEs during Placebo treatment. AEs in both groups were generally representative of common complaints in the CF population. AEs were more common during Placebo (71%) than Creon (50%) treatment. The most common AEs during Creon treatment were abdominal pain and flatulence (9% each) followed by dizziness, headache, cough and nasal congestion (6% each). The most common AEs during Placebo treatment were abdominal pain, flatulence, and headache (26% each). The fewer AEs overall during Creon treatment likely reflects that Creon was efficacious in decreasing gastrointestinal symptoms. AEs occurring in $\geq$2 patients in either treatment group during the study are summarized in Table 23.

Table 23: AEs occuring in >2 Patients in Either Treatment Group in the Pivotal Study

		Creon	Placebo
System, Organ, Class	**Preferred Term**	**N=32 (%)**	**N=31 (%)**
Gastrointestinal disorders	Abnormal feces	1 (3)	6 (19)
	Flatulence	3 (9)	8 (26)
	Abdominal pain	3 (9)	8 (26)
	Abdominal pain upper	0	3 (10)
Investigations	Weight decreased	1 (3)	2 (6)
Nervous system disorders	Headache	2 (6)	8 (26)
	Dizziness	2 (6)	0
Respiratory, thoracic and mediastinal disorders	Cough	2 (6)	0
	Patients with Any AE	**16 (50)**	**22 (71)**

The Reviewer believes the lower incidence of AEs in the Creon group is due to the lower incidence of gastrointestinal complaints in this group compared to placebo, paralleling changes in secondary efficacy endpoints (Patient Global Impression) discussed in section 5.3.5 of this document. A list all AEs reported in the Pivotal Study is located in Table 29 in Appendix 9.4 of this document.

7.4.2 Laboratory Findings

The Pivotal lab dataset was thoroughly reviewed and changes in clinical lab findings that were classified as AEs were reported in the AE dataset.

Three patients with normal Screening absolute neutrophil counts (ANC; normal >1,500 x $10^{\wedge 3}$cells/uL) experienced potentially meaningful decreases in neutrophil count with Creon treatment. Patient 0031-00001 had a Baseline ANC of 7,640, which decreased to 620 with exposure to Creon in the first cross-over period and was normal from the end of WO (10,950) through the end of the study (6,860). This patient's low ANC occurred concomitantly with a decreased WBC count (normal <4500 x $10^{\wedge 3}$cells/uL). This ANC meets the common clinical definition of moderate neutropenia [(severe <500, moderate 501 to 999, and mild 1,000 to 1,500 x $10^{\wedge 3}$cells/microL)]. The Sponsor notes that the patient was taking a macrolide antibiotic at the time. Patients 0010-00007 and 0025-00002 had normal ANCs at Screening through CO1 (Placebo) and experienced decreased ANCs during CO2 (Creon). Decreases in these two patients did not meet the clinical definition of absolute neutropenia (Table 24).

Table 24: Absolute Neutrophil and White Blood Cell (N/W) Count by Creon or Placebo (P) Treatment

Patient ID	Sequence	N/W	Screening	End of CO1	End of Washout	End of CO 2
0031-00001	Creon→P	N	7,640	620	10,950	6,860
		W	10,600	2,900	14,100	9,300
0010-00007	P→Creon	N	4,430	3,530	4,470	1,570
		W	8,700	7,900	9,500	6,600
0025-00002	P→Creon	N	5,920	7,760	3,610	1,660
		W	8,800	11,200	6,400	5,100

Neutropenia is not classically associated with PEP treatment. Review of the AE dataset and the clinical laboratory dataset did not reveal other factors which may have precipitated these

findings, such as viral illness. The small patient population and short duration of the study limits the ability to draw conclusion; however, a causal relationship by Creon can not be ruled out based on this placebo-controlled trial. The neutropenia finding should be included in labeling.

There were no other clinically meaningful differences in clinical laboratory findings between Creon and placebo treatment. Serum uric acid analyses are shown for illustrative purposes due to known dose-related risk of hyperuricemia.

At Screening, uric acid levels were similar in the two treatment sequences (mean 6.0 and 6.1 mg/dL; median 5.7 and 5.6 mg/dL). At the end of CO1, mean uric acid was similar (6.1 and 6.2 mg/dL), but median uric acid was higher in placebo-treated patients than Creon treated patients (6.6 vs. 5.9 mg/dL, respectively). At the end of CO2 mean uric acid values lower in Creon- than placebo-treated patients (5.8 vs. 6.0 mg/dl) but median uric acid was higher in Creon than placebo-treated patients (6.3 vs. 6.0 mg/dL, respectively). These results are shown in Table 25.

Table 25: Serum Uric Acid (mg/dL) by Treatment and Sequence

Visit	Screening	End of First Treatment Period	End of Washout Period	End of Second Treatment Period
Sequence	**Creon→Placebo**		**Placebo→Creon**	
Creon	N=16	N=16	N=16	N=16
Sample Mean (SD)	6.0 (1.1)	6.1 (1.3)	6.1 (1.6)	5.8 (1.5)
Median	5.7	5.9	6.1	6.3
Sequence	**Placebo→Creon**		**Creon→Placebo**	
Placebo	N=16	N=16	N=15	N=15
Sample Mean (SD)	6.1 (1.6)	6.2 (1.6)	6.0 (1.0)	6.0 (0.9)
Median	5.6	6.6	5.9	6.0

In summary, there was no consistent difference in uric acid levels between Creon and placebo; however, risk of hyperuricemia should be included in labeling. There was no consistent difference in urine acid levels from spot urine analyses between Creon and placebo (data not shown) but 24-hour urine collections for uric acid clearance were not performed.

In conclusion, there were no consistent trends in any laboratory findings. Additionally, the association of hyperuricemia with PEP treatment is not disproved and should be addressed in labeling. The occurrence of neutropenia with Creon treatment should be addressed in labeling.

7.4.3 Vital Signs

Changes in vital signs that qualified as AEs were reported in the AE dataset. An exhaustive review of the vital sign dataset was performed and there were no notable or consistent findings between Creon and Placebo treatment (data not shown).

7.4.4 Electrocardiograms (ECGs)

Creon and Other PEPs are a mixture of large enzyme moieties and are not systemically absorbed. Therefore, interference with electrophysiological functions are not expected, ECGs were not systematically performed, and a TQT study is not expected to be requested.

7.4.5 Special Safety Studies

No other special safety studies were performed as part of the Creon development plan.

7.4.6 Immunogenicity

Creon and Other PEPs are a mixture of large enzyme moieties, are not systemically absorbed, and are not felt to be immunogenic. Therefore, immunogenicity studies were not part of the Creon development plan.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The Pivotal Study was a single dosage study adjusted for daily dietary fat intake which, in addition to the small study size, limited ability to perform clinically meaningful safety assessments by dose. This Reviewer performed an exploratory assessment of AEs by dose above and below the specified dose 4,000 Lu/gram of fat per day and above and below 10,000 Lu/kg/day dose explorations. These assessments did not reveal meaningful differences in AEs dose (data not shown).

PEPs are dosed to achieve improved clinical signs (CFA) and symptoms such as decreased bloating, decreased stool frequency, and increased stool consistency. As detailed in section 5.3.1.5 of this Review, FC risk is related to maximal dose and duration of treatment, and while no lipase dose is without risk, relative risk of FC increases with doses above 24,000 Lu/kg/day (6,000 Lu/kg/meal).[1]

In recognition of these risks, CFF guidelines recommend not exceeding 10,000 Lu/kg/day, divided equally across 3 meals and 2 to 4 snacks per day [equivalent to 2,500 Lu/kg/meal]. To address appropriate physiologic dosing in Lu/gram fat/day, the CF Guidelines recommend a maximum dose of 4,000 Lu/gram fat/day; the same dose evaluated in the Pivotal Study.

Labeling should be consistent with CFF dosing guidelines, which are located in section 7.6.4 of this review.

7.5.2 Time Dependency for Adverse Events

The short duration of the Pivotal Study did not allow for explorations of time dependant AEs such as FC.

Safety data from multi-dose randomized, blinded, placebo-controlled studies of CMP from one to 16 weeks in duration were reviewed during the prior review cycles (see Clinical Review, Ethan D. Hausman, MD, August 16, 2007; Fathia Gibril, MD, December 9, 2003) and no time dependant AEs were noted.

This Reviewer concludes that since bridging to CMP has not been demonstrated, no clinical inferences can be drawn regarding the incidence of time dependent AEs with TbMP.

7.5.3 Drug-Demographic Interactions

Drug-demographic interactions were not part of the Creon development plan. All patients in the Pivotal Study were Caucasian and exploration of AEs by race or ethnic background could not be performed. The severity of EPI in CF is related specific mutations which likely have racial/ethnic differences; however, there is no information to indicate race has an independent effect.

7.5.4 Drug-Disease Interactions

Drug-disease interactions were not part of the Creon development plan.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not part of the Creon development plan.

Drug affecting gastrointestinal pH (antacids and H2-blockers) and motility (erythromycin) may affect activation of lipases, proteases, and amylases in PEPs. This information may be included in labeling.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Creon and other PEPs are mixtures of large enzyme moieties, are not systemically absorbed, and are not felt to be immunogenic. Therefore, carcinogenicity studies were not part of the Creon development plan.

7.6.2 Human Reproduction and Pregnancy Data

No studies with Creon were conducted in pregnant women.

It is likely that Creon products will be used by pregnant women and women of reproductive potential. Future labeling should address safety in pregnancy. The Pharmaco-Toxicology review team recommends Pregnancy "Category C"; studies not conducted. This Reviewer concurs with this recommendation.

7.6.3 Pediatrics and Effect on Growth

PEPs are believed to a have a positive effect on pediatric growth. [5, 13] The Pivotal Study was a short-term study and long-term growth and development were not assessed. FDA recognizes that performance of such long-term studies may not be practical in the context of pre-market development of PEPs due to the long marketing history that supports safety and efficacy of the drug-class.[4]

7.6.3.1 Other Pediatric Issues

The Pediatric Review Committee (PeRC) and the DGP met to discuss available clinical data from completed studies of the TbMP, the CFF Dose Guidelines, available literature addressing the balance of risk/benefit of PEPs, and manufacturing/CMC issues. The PeRC recommended that safety and efficacy in children could be extrapolated; however, this would not relieve the Applicant from developing age appropriate formulations or dose forms.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

PEPs are not systemically absorbed. An important safety issue regarding PEP use is fibrosing colonopathy (FC). The etiology of FC has not been definitively established, but is thought to be associated with high dose lipase exposure, although it is possible that risk is due to excipients. In order to optimize therapy while minimizing the risk of FC, the Cystic Fibrosis Foundation (CFF), in conjunction with the FDA, recommends doses as described below.[2,3,4,5]

Dose schedule for full meals:

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.
- Children $\leq$4 years old eating soft or solid foods: begin with 1,000 USP lipase units/kg/meal.
- Children >4 years old: begin with 500 lipase units/kg/meal.
- Doses in excess of 2,500 USP lipase units/kg/meal should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to significantly improve a documented low coefficient of fat absorption.
- The recommended per meal dose should be halved when ingesting snacks.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with fibrosing colonopathy and should not be used.

7.7 Additional Submissions

This TbMP was submitted for review under NDA 20-725. It is also currently under investigation under IND 47,546. Three planned or ongoing clinical trials are summarized below:

13 Baker SS, MD, Borowitz D, Duffy L, Fitzpatrick L, et al., Pancreatic Enzyme Therapy and Clinical Outcomes in Patients with Cystic Fibrosis. J Pediatr 2005; 146:189-93.

- Study S245.3.127 is evaluating TbMP in children with CF-related EPI ages 7 through 11years. The Applicant notified the Division that this study complete and the final study report will be submitted to the NDA in June 2009.
- Study S245.3.128 will evaluate TbMP children with CF-related EPI ages 1 month through 6 years. The protocol has been submitted and reviewed. Enrollment is expected to begin in summer of 2009 and the final study report will be submitted in July 2010.
- Study 245.3.124 is evaluating TbMP in adult patients with EPI due to chronic pancreatitis or pancreatectomy and the final study report will be submitted in September 2009.

The clinical results of these studies will be submitted to the NDA at a later date for review in consideration of future labeling.

8 Postmarketing Experience

There is no post-marketing experience with the to-be-marketed product.

Enteric-coated Creon microspheres (MS) were introduced in Germany in 1982 and Creon minimicrospheres (MMS) debuted in 1993. Creon MS was replaced in the Rest of the World (ROW; includes all countries where Creon MMS is/was marketed) by Creon MMS in 2003. The Applicant states that as of 30-April-2008, marketing authorization for the CMP version of Creon MMS had been granted in 76 non-US countries. As of the date of submission of this NDA update, no Creon MMS product had been withdrawn for safety concerns.

The period of reporting for the ISS update was 01-July-2006 through 31-March-2008. The Applicant states that since the prior ISS update received in November 2006, a total of 328 postmarketing AE reports were received in 166 individual patients treated with varying strengths and formulations of the CMP. Fifty five of the reports were for SAEs.

Specific product formulations were not identified for most post-market AEs. Products in distributions throughout the time of the ISS update include the following: Creon (Pancrelipase) minimicrospheres, Creon (Pancreatin), Kreon (Pancreatin), Pankreon (Pancreatin), Pankreon forte (Pancreatin), Pankerozym (Pancreatin), Pancrin (Pancreatin), and Papine (Pancreatin).

Deaths and AEs from the post-marketing experience are presented descriptively. Incidence rates of deaths and AEs in the post-marketing experience cannot be determined because the number of exposed patients (the denominator population) is unknown. Individual doses can not be determined.

The two newly reported deaths occuring during CMP post-marketing experience, are summarized below:

- Report US-SOLVAY-00208000980: This patient was an 82-year-old woman with a history of celiac disease who was hospitalized because of a “gallbladder attack” and who was then taken off Creon CMP and all oral nutrition for five days. The patient became

malnourished and died from myocardial infarction one month later. The report stated the relationship to Creon products was unlikely.

- Report DE-SOLVAY-00306003397: This patient was a 64-year-old man receiving Creon CMP for 1 ½ years due to gastrectomy. He began to experience dyspnea on exertion and dry cough. He died to months later and the cause of death was not reported. Further information is not available. The report stated the relationship to Creon products was unlikely.

The most serious adverse events reported in the CMP post-marketing experience included fibrosing colonopathy, distal intestinal obstruction syndrome (DIOS), severe allergic reactions including anaphylaxis, asthma, hives and pruritus, and recurrence of pre-existing carcinoma. The most commonly received post-market AEs reported by MedDRA System Organ Classes (SOC) were gastrointestinal disorders (44% of reports), skin and subcutaneous tissue disorders (11% of reports), investigations (5% of reports), nervous system disorders (5% or reports), and immune system disorders (2% of reports). These findings are similar to prior reviews (Ethan D. Hausman MD, August 16, 2007).

The post-market update received with the 2006 Complete Response included one report of histologically confirmed fibrosing colonopathy (FC) in a 25 year-old man with CF who had at least eight years of exposure to different PEP formulations administered at unstated daily doses. He discontinued all PEP therapy three years prior to the diagnosis of FC. Of events possibly related to FC there was one report each of intestinal obstruction and colitis. There are no newly reported cases of FC in the ISS update (CMP).

There were three reports of DIOS with CMP treatment reported in the 2006 Complete Response, and eight newly received post-market reports of DIOS. All cases were in children with CF treated with CMP. No dose information is available for these reports of DIOS. Additional clinical information is not available.

The risk of FC is well described in the literature and is to be addressed in labeling.

In conclusion, the current update to the post-marketing safety report is substantially similar to findings of prior clinical reviews and there were no new clinically meaningful findings.

9 Appendices

9.1 Literature Review/References

References in the body of this document are provided as footnotes. The following references address the following: use of CFA and other measures of stool fat used in patients with EPI, short term placebo-controlled and treatment controlled trials in patients with EPI, treatment guidelines for patients with CF- and CP-related EPI including the need for periodic fat soluble vitamin monitoring. References are presented with short synopses.

Additional references with synopses where noted:

14. 69 FR 23410 citing the 19-November-1978 Advisory Review Panel on Over-the-Counter Miscellaneous Internal Drug Products. Selected articles referenced by the Advisory Committee include:

15. Graham, DY. Enzyme Replacement Therapy of Exocrine Pancreatic Insufficiency in Man, NEJM, 23: 1314-1317, 1977.—*The investigator assessed the enzyme activity of 16 PEPs and found that in vitro lipase activity correlated with in vivo potency for reducing steatorrhea. Reduction in steatorrhea in tables and capsules was 56% and 49%, respectively. Higher gastric/duodenal pH associated with greater reduction in steatorrhea*.

16. Littman, A and Hanscom DH. Pancreatic extracts. NEJM, 281:201-204, 1969.—*This is a review of clinical practice at the time for patients with EPI treated with PEPs. The article provides dose guidance in number of pills per day and pill mass (grams) per day and the information is not readily translated into current dose guidelines in lipase unit/kg/day or lipase units/gram dietary fat ingested per day. The article summarizes limited data for change in CFA in patients with no treatment compared to their CFA during PEP treatment. CFA increased with PEP treatment.*

17. Kalser MH, Leite CA and Warren WD. Fat Assimilation after Massive Distal Pancreatectomy. NEJM, 279(11):570-576, 1968.—*This article provides information on fat assimilation in 7 patients with EPI due to distal pancreatectomy at baseline and with PEP replacement. Non-treatment CFA was Mean CFA increased 14% in 4 patients with 95% resection compared to non treatment. Daily lipase dose was not provided and can not be derived from the information in the article.*

18. Jordan PH and Grossman MI. Effect of Dosage Schedule on the Efficacy of Substitution Therapy in Pancreatic Insufficiency. Gastroenterology, 36:447-451, 1959.—*This article provides information on both fat and nitrogen absorption in 11 patients with EPI due to chronic pancreatitis. Dose was 8 gram/day of PEP formulation; however dose in lipase units could not be determined from the information provided. PEPs were provided either as hourly or thrice daily doses. PEP treatment was associated with reduction in stool fat and stool nitrogen but change in CFA and coefficient of nitrogen absorption was not provided.*

19. Marks IN, Bank S, Airth EM. Pancreatic Replacement Therapy in the Treatment of Pancreatic Steatorrhea, Gut, 4:217-222, 1963.—*Steatorrhea was improved in 11 patients with EPI and steatorrhea treated with Viokase. Steatorrhea was not improved in 5 patients with post-gastrectomy or primary intestinal causes of steatorrhea*.

Other references

20. Rovner AJ, Stallings VA, et al. Vitamin D insufficiency in children, adolescents, and young adults with cystic fibrosis despite routine oral supplementation1Am J Clin Nutr 2007;86:1694-1699.—*Study comparing Vitamin D status in children and adults with CF (N=101) compared to healthy controls (N=177). The odds of vitamin D insufficiency in the CF group, compared with the healthy reference group, were 1.2 (95% CI: 1.1, 1.3).*

21. Borowitz D, et al. Study of a novel pancreatic enzyme replacement therapy in pancreatic insufficient subjects with cystic fibrosis. J Pediatr 2006; 149:658-662.—*Treatment control (low, medium, high dose) trial of patients with CF-related EPI with a microbially-derived lipase, protease, and amylase PEP. In high-dose treated patients increase in CFA was 31% in patients with non-treatment CFA ≤ 40% and 8% in patients with non-treatment CFA >40% (P < .0001).*

22. Stern RC, et al. A Comparison of the Efficacy and Tolerance of Pancrelipase and Placebo in the Treatment of Steatorrhea in Cystic Fibrosis Patients with Clinical Exocrine Pancreatic Insufficiency. Am J. Gastroenterol 2000; 95: 1932-1938.—*Short-term randomized-withdrawal study of safety and efficacy in 97 adults and children (≥7 years old) with CF-related EPI treated PEPs. On randomized, blinded withdrawal, CFA dropped 35 to 37% in patients switched to placebo compared with a drop of 3 to 5 % in patients who remained on PEP treatment. Adverse events were predominantly related to the gastrointestinal system and were more common during placebo-treatment.*

23. O'Keefe SJ, Cariem AK, Levy M. The exacerbation of Pancreatic Endocrine dysfunction by Potent Pancreatic Exocrine Supplements in Patients with Chronic Pancreatitis. J Clin Gastroenterol 2001; 32:319-323. —*Short-term placebo-controlled study of pancrelipase in 29 patients with chronic pancreatitis (CP)-related EPI. Stool volume was lower and CFA was higher in the active treatment group than the placebo group (81% SD 4 vs. 54% SD 10%). No comment on safety.*

24. Safdi M, Bekal PK, Martin S, Saeed Z et. al.. The Effects of Oral Pancreatic Enzymes (Creon 10 Capsule) on Steatorrhea: a Multicenter, Placebo-controlled, Parallel Group Trial in Subjects with Chronic Pancreatitis. Pancreas 2006; 33: 156-162. —*Short-term placebo-controlled study in patients with CP-related EPI. Creon treated patients (N=13) had a greater increase in CFA than placebo treated patients (N=14)(37% vs. 12%) and there were fewer adverse events in Creon-treated patients.*

25. Patchell CJ, Desai M, et al. Creon 10,000 Minimicrospheres vs. Creon 8,000 Microspheres – an open randomized Crossover Preference Study. J. Cystic Fibrosis 1 (2002):287-291.—*This was a short-term open-label, treatment control cross-over study of 59 children with CF-related EPI, ages 3 to 17 years. Median lipase dose was 6689 lipase units/kg/day in the Creon 8,000 group and 8527 lipase units/kg/day in the Creon 10,000 group. Mean CFA was 94% in the Creon 8,000 group and 91% in the Creon 10,000 group. No treatment differences in stool frequency, stool consistency, flatulence and abdominal pain were reported.*

26. Konstan MW, Stern RC, et al. Ultrase MT12 and Ultrase MT20 in the Treatment of Exocrine Pancreatic Insuffficiency in Cystic Fibrosis: safety and Efficacy. Aliment Pharmacol Ther 2004; 20:1365-1371.—*These were two short-term placebo-controlled study of Ultrase MT12 (N=22) and Ultrase MT 20 (N=25) in patients with CF-related EPI ages 7 to 36 years. In both studies, CFA was approximately 30% higher during Ultrase treatment compared to placebo. Adverse events during Ultrase and placebo-treatment were similar.*

27. Proesmans M and De Boeck K. Omeprazole, a Proton Pump Inhibitor, Improves Residual Steatorrhoea in Cystic Fibrosis Patients Treated with High Dose Pancreatic Enzymes. Eur J Pediatr. 2003; 162: 760-763.—*This study evaluated the effect of proton pump inhibitors (PPIs) on CFA in patients with CF-related EPI (N=15), ages 3 to 16 years, treated with PEPs. Treatment with PPI was associated with increased CFA of 7%*.

28. Kalnins D, Corey M, et al. Combining Unprotected Pancreatic Enzymes with pH-sensitive Enteric-coated Microspheres Does Not Improve Nutrient Digestion in Patients with Cystic Fibrosis. J Pediatr 2005; 146:489-493.—*In this short-term clinical study of 14 patients with CF-related EPI, ages l.9 to 13.4 years, there was no difference in fat absorption with addition of enteric-coated preparations when PEP dose was otherwise held constant.*

29. Munck A, Duhamel JF, Lamireau T, Le Luyer B et. al., Pancreatic enzyme replacement therapy for young cystic fibrosis patients. J Cystic Fibrosis 2009: 8:14-18.—*This was a short-term, cross-over study of 40 patients with CF-related EPI, ages 6 to 36 months old, treated with Creon 10,000 and Creon for children (a non-marketed formulation of "loose granules"). Mean lipase dose was 4488 lipase units/kg/day.* Mean CFA was 79%, with no non-treatment CFA for comparison. Safety findings were similar during each treatment and SAEs were reportedly unrelated to treatment (bronchial infection and otitis media).

30. Nassif EG, Younoszai MK, Weinberger MM, Nassif CM. Comparative Effects of Antacids, Enteric Coating, and Bile Salts on the Efficacy of Oral Pancreatic Enzyme Therapy in Cystic Fibrosis. J. Pediatrics 1981:Vol 98 No. 2:320-323.— *A case series of 11 children with CF-related EPI, ages 8 to 18 years, treated with Cotazym, Cotazym-65B, Cotazym + Maalox, and Pancrease. Daily lipase dose, CFA and change in CFA were not provided and could not be derived from information in the publication. Safety information was limited to discussion of the risk of hyperuricemia.*

31. Santini B, Antonelli M, Battistini A, Bertasi M, et al. Comparison of Two Enteric Coated Microsphere Preparations in the Treatment of Pancreatic Exocrine Insufficiency Caused by Cystic Fibrosis. Digest Liver Dis 2000; 32:406-411.—*This was a short-term cross-over study assessing preference for two PEPs (including a no-longer marketed formulation of Creon) in 60 patients with CF-related EPI, ages ≥6 years. Patients ingested a standardized daily diet of at least 2 g fat/kg body weight and ingested 1000 units lipase/g fat of diet. CFA with both treatments were similar. No serious adverse events were reported in the article.*

32. Vyas H, Matthew DJ, Milla PJ. A comparison of enteric coated microspheres with enteric coated tablet pancreatic enzyme preparations in cystic fibrosis. Eur J Pediatr 1990;149:241-243.—*Short-term cross-over study in 20 patients with CF-related EPI, reporting superior control of steatorrhea and stool frequency during enteric-coated microsphere treatment rather than enteric-coated tablet treatment*.

33. Thomson M, Clague A, Cleghorn GJ, Shepherd RW. Comparative in vitro and in vivo studies of enteric-coated pancrelipase preparations for pancreatic insufficiency. J Pediatr Gastroenterol Nutr 1993;17:407-413.— *In a study of 3 commercially available PEPs, in vitro enzyme potency varied markedly between batches of the same brand, and also a decline of up to 20% in amylase, lipase, and trypsin activity was noted over an 8-month period for each batch.*

34. Robinson PJ, Olinsky A, Smith AL, Chitravanshi SB. High compared with standard dose lipase pancreatic supplement. Arch Dis Child 1989;64:143-145.—*This short-term cross-over study compared two enteric coated PEPs (Cotazym-S-Forte 10 000 BP lipase units per capsule vs. Pancrease 5000 BP lipase units per capsule) in 30 children with CF-related EPI ages 1.3 to 13.8 years. Degree of fat malabsorption was similar (12% and 13%) and no adverse events were reported in the publication.*

35. Petersen W, Heilman C, Garne S. Pancreatic enzyme supplementation as acid-resistant microspheres versus enteric-coated granules in cystic fibrosis. Acta Paediatr Scand 1987;76:66-69.—*This was a short-term, blinded, cross-over study of two enteric-coated PEPs in 11 patients with CF-related EPI younger than 12 years old. Differences in CFA between treatments were not statistically significant.*

36. Morrison G, Morrison JM, Redmond AOB, et al. Comparison between a standard pancreatic supplement and a high enzyme preparation in cystic fibrosis. Aliment Pharmacol Ther 1992;6:549-555.— *This was a short-term study of a two PEPs with different lipase concentrations. Patients were treated with equivalent lipase units/kg body weight/day and CFA between treatments was not statistically different (83% vs. 84%). No "significant" adverse events were reported in the publication.*

37. Gow R, Bradbear R, Francis P, Shepherd R. Comparative study of varying regimens to improve steatorrhoea and creatorrhoea in cystic fibrosis: Effectiveness of an enteric-coated preparation with and without antacids and cimetidine. Lancet 1981; 2(8255):1071-1074.— *This study compared four PEP treatment regimens in 11 children with EPI-related C, ages 6 through 13 years old. Treatments included sequential treatments with 14 days each of a non-enteric coated PEP (Cotazym), a "pH-sensitive" enteric-coated PEP (Pancrease), Pancrease with cimetidine, and Pancrease with antacid suspension. Dose in lipase units/kg of body weight per day was not reported. Stool fat excretion was greatest during Cotazym treatment and least with Pancrease/cimetidine. No drug-related side-effect were reported.*

38. Goodchild MC, Sagaro E, Brown GA et al. Comparative trial of Pancrex V Forte and Nutrizym in treatment of malabsorption in cystic fibrosis. Br Med J 1974;3:712-714.—

This was a short-term study of a two PEPs in 12 children with CF-related EPI. Fecal and urine fat excretion were similar. Dose was ad hoc, and dose in lipase unit/kg/day was not reported and could not be derived from information in the publication.

39. George DR, Pinero R, Miller AB, Toskes PP, et al. Comparison of two pancreatic enzyme supplements in patients with cystic fibrosis. Adv Ther 1990;7(3):109-118.—*This was a 20 day treatment control study of two PEPs; 10 days of each treatment. Diet was held intake was held constant during both treatment periods. During the first treatment period, patients ingested their usual PEP (Pancrease) at their usual physician directed dose (i.e., ad hoc dose), and patients were assessed for 72-hour CFA and clinical symptoms. Patients were then switched to a no-longer marketed PEP at an equivalent lipase/kg/day dose (not specified) for 10 days and were again assessed 72-hour CFA and clinical symptoms. 72-hour CFA and clinical symptoms were similar in the two treatment periods. Adverse events were reported to be mild and predominantly gastrointestinal-related.*

40. Elliott RB, Escobar LC, Lees HR, Akroyd RM, Reilly HC. A comparison of two pancreatin microsphere preparations in cystic fibrosis. NZ Med J 1992. 105(930):107-108.— *This was a short-term cross-over study of 2 PEPs in children with CF-related EPI. At similar lipase doses, patients had equivalent CFA.*

41. Carroccio A, Pardo F, Montalto, Iapichino L, et al. Use of famotidine in severe exocrine pancreatic insufficiency with persistent maldigestion on enzymatic replacement therapy. Dig Dis Sci 1992;37(9):1441-1446.— *This 6-month study of 10 patients with CF-related EPI assessed change in CFA and clinical symptoms in patients treated PEPs with and without famotidine. Concurrent famotidine treatment was associated with improved CFA.*

42. Bowler IM, Wolfe SP, Owens et al. A double blind lipase for lipase comparison of a high lipase and standard pancreatic enzyme preparation in cystic fibrosis. Arch Dis Child 1993;68:227-230.— *This was a short term study of 18 patients with CF-related EPI treated with 2 PEP formulations. Dose in lipase unit/kg/day was not reported and could not be derived from the information provided.*

43. Beverley DW, Kelleher J, MacDonald A et al. Comparison of four pancreatic extracts in cystic fibrosis. Arch Dis Child 1987;62:564-568.— *This was a 7-week sequential treatment study of 4 commercially available PEPs in 19 patients with CF-related EPI, ages 6 to 20 years. Dietary fat was held constant across treatment periods and there was no statistically significant difference in CFA between treatments. Dose in lipase units/kg/day was not reported and could not be derived from the information provided. Adverse events were predominantly gastrointestinal in nature.*

44. Colombo C, Maiavacca R, Ronchi M et al. The steatocrit: A simple method for monitoring fat malabsorption in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 1987;6(6):926-930.— *This study demonstrated an inverse correlation of steatocrit with PEP treatment in 107 patients with CF-related EPI (1.7% SD 1.2)vs. 110 health controls (0.7 to 1%). In a subset of 74 CF patients in whom both steatocrit and CFA were*

available, steatocrit was directly correlated to the coefficient of fat excretion (r 0.93: P < 0.001).

45. Beker LT, Fink RJ, Shamsa FH, Chaney HR, et al. Comparison of weight-based dosages of enteric-coated microtablet enzyme preparations in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 1994;19(2):191-197.— *This was a short-term cross-over study of low-dose (500 lipase unit/kg body weight/meal) and high-dose (1,500 lipase unit/kg body weight/meal) with dietary fat of approximately 100gram/day. In patients with high fecal fat excretion at the start of the study, higher doses were associated with greater increase in CFA.*

46. Ansaldi-Balocco N, Santini B, Sarchi C. Efficacy of pancreatic enzyme supplementation in children with cystic fibrosis: Comparison of two preparations by random crossover study and a retrospective study of the same patients at two different ages. J Pediatr Gastroenterol Nutr 1988;7(Suppl 1):S40-S45.—*This article reports a prospective open-label cross-over study of 2 PEP formulations in patients with CF-related EPI, and a case control study of patients with CF-related EPI treated for 3 months compared to a historical control group of patients with CF-related EPI. No adverse reactions were seen with either of the enzyme preparations used in these studies.*

47. Schall JI, Bentley T, Stallings VA. Meal Patterns, dietary fat intake and pancreatic enzyme use in preadolescent children with cystic fibrosis. J Pediatr Gastroenterol Nutr 2006;43(5):651-659.— *This article describes the "usual" short-term pattern of diet and PEP intake in 75 children 8 to 11 years old with CF-related EPI. Approximately 85% of patients adhered to doses of ≤2,500 lipase units/kg/meal; however, adherence to recommended dose with snacks was 58% to 68%. The publication is also a good source for normative growth parameters in CF-patients for the ages studied.*

48. Sugai E, Srur G, Vazquez et al. Steatocrit: A reliable semiquantitative method for detection of steatorrhea. J Clin Gastroenterol 1994;19(3):206-209.— *The study compared two methods for fecal fat detection. Of 148 stool samples, 77 had increased fat (>7 g/day). The candidate method (steatocrit) had a sensitivity of 87%, specificity of 97%, and positive and negative predictive values of 97 and 87%, respectively compared to the reference method. Sensitivity increased with increased fat content in stool.*

49. Van den Neucker AM, Forget PP, van Kreel B. Lipid, nitrogen, water and energy content of a single stool sample in healthy children and children with cystic fibrosis. Eur J Pediatr 2003;162:764-766.—*Fecal fat excretion and acid steatocrit results were determined in 42 children, half with and half without fat malabsorption. Acid steatocrit results correlated significantly with both fecal fat excretion (p < 0.01) and fecal fat concentration (p < 0.001). Sensitivity and specificity of the acid steatocrit for the diagnosis of malabsorption were 90% and 100%, respectively. We consider the acid steatocrit method useful for the screening and monitoring of patients with steatorrhea.*

50. Walters MP, Kelleher J, Gilbert J, Littlewood JM. Clinical monitoring of steatorrhea in cystic fibrosis. Arch Dis Child 1990;65(1):99-102.—*This was a qualitative/semi-*

quantitative assessment of three methods of stool fat analysis included biochemical analysis (gold standard at the time), steatocrit, and microscopy in 100 patients with CF-related EPI, ages 6 months to 27 years, with symptomatic steatorrhea. When dietary fat intake was fixed (grams/fat intake/day not provided), microscopy correlated well with biochemical analysis. Methodological deficiencies with steatocrit precluded meaningful analyses and meaningful comparisons to biochemical methods.

51. Wagner MH, Bowser EK, Sherman JM, Francisco MP, et al. Comparison of steatocrit and fat absorption in persons with cystic fibrosis. J Pediatr Gastroenterol Nutr 2002;35:202-205.—*This was a comparison of 72 hour CFA and four methods of steatocrit analysis performed on 49 stool samples from 27 patients with CF-related EPI. CFA and acid steatocrit had a statistically significant correlation (p=0.033). Standard, dilute, and dilute acid steatocrit did not have "good" correlation with CFA (correlation coefficient from -0.045 to -0.491).*

52. Van den Neucker A, Pestel N, Tran TMD, Forget PPH, et al. Clinical use of acid steatocrit. Acta Paediatr 1997;86:466-469.—*This was a comparison of CFA and acid steatocrit in 42 children, 6 ½ months and 18 years old. Approximately ½the patients had CF-related EPI, and the other ½ of the patients had other disorders without evidence of steatorrhea. Single and multiple specimen acid steatocrit both correlated with fat concentration [r=0.82, p<0.001]; however, multiple specimen acid steatocrit had a superior correlation with fat excretion [r=0.68, p<0.001] than single specimen steatocrit [r=0.4, p<0.01].*

53. Van den Neucker AM, Kerkvliet EM, Theunissen PMVM, Forget P-Ph. Acid steatocrit: a reliable screening tool for steatorrhoea. Acta Paediatr 2001;90:873-875.—*This study compared acid steatocrit from 166 children (34 with EPI-related CF, 16 with untreated celiac disease, 40 patients with other gastrointestinal disorders, 26 patients with asthma, and 50 healthy children). The median values (5th–95th percentile) of AS results were 3.3% (0.0–21%) for healthy children, 4.5% (1.8–22.5%) for asthma patients, 24.7% (2.6–68.2%) for treated CF patients with exocrine pancreatic insufficiency, 19.8% (3–77.7%) for untreated CD patients and 5.5% (1.8–29%) for patients with various gastrointestinal diseases. In conclusion, median acid steatocrit values are higher in patients with EPI; however, median acid steatocrit values in children with CF-related EPI overlap with median values of healthy children.*

54. Baker SS, Borowitz D, Duffy L, Fitzpatrick L, et al. Pancreatic Enzyme Therapy and Clinical Outcomes in Patients with Cystic Fibrosis. J Pediatrics 2005; 146:189-193.—*In a retrospective review of 1215 patients with CF, included 1131 patients treated with PEPs, approximately 15% of patients had pre-treatment assessment of fat absorption. When patients with EPI (88.5%) were compared to patients without EPI (11.5%), there was no difference in growth outcomes. The article concludes that PEP treatment is not associated with improved growth. That conclusion is faulty since the appropriate comparison could not be performed from the data provided: Patients with EPI treated with PEPs vs. not treated with PEPs. This author concludes that no clinical conclusions may be drawn from the data.*

55. Siret D, Bretaudeau G, Branger B, Dabadie A, et al. Comparing the Clinical Evolution of Cystic Fibrosis Screened Neonatally to that of Cystic Fibrosis Diagnosed from Clinical Symptoms: A 10-Year Retrospective Study in a French Region (Brittany). Pediatric Pulmonology 2003; 35:342-349.—*This report compares clinical data from patients with CF (irrespective of EPI) in France who were diagnosed either by clinical presentation (N=36) or through newborn screening (N=77). Mean age at diagnosis was lower in screened patients (38 days vs. 472 days), as was mean age at first PEP supplementation (1.7 months vs.15.9 months). The proportion of children who were hospitalized was higher in non-screened patients (86% vs. 49%). In the screened group, Z-scores for weight and height were better in the first years of life, Z-score for height was better at 5 years, and Z-score for weight was better at 8 years. Deaths were greater in non-screened group compared to the screened group (3/36 vs. 0/77).*

56. Farrell PM, Kosorok MR, Laxova A, Shen G, et al. Nutritional Benefits of Neonatal Screening for Cystic Fibrosis. NEJM.1997, 337(14): 963-969.—*This report compares the nutritional status over 10 years in a sub-population US patients with CF who were diagnosed either by clinical presentation (N=40) or through newborn screening [(N=56; 18 of 74 patients were excluded from this comparator group for meconium ilues or other reasons including indeterminate screening test results]. At diagnosis, the screened group (mean age at diagnosis 12 weeks) had significantly higher values for the following indices that the non-screened groups (mean age at diagnosis 72 weeks: height or length (44%-ile vs. 25%-ile, weight (36%-ile vs. 22%-ile), and head-circumference percentile (52%-ile vs. 32%-ile); p<0.01 for each or the preceding results.*

57. Steinkamp G, Weidemann, et al. Relationship Between Nutritional Status and Lung Function in Cystic Fibrosis: Cross Sectional and Longitudinal Analyses from the German CF Quality Assurance (CFQA) Project. Thorax 2002; 57(7):596-601.—*This was a cross-sectional study assessing a cohort of 3,298 patients with CF, 2 years and older. Patients were grouped by the presence or absence of malnutrition (wasting and/or stunting) growth assessments were compared at 2 and 3 years from "baseline". Patients with malnutrition had significantly lower (poorer) mean values of vital capacity, arterial oxygen tension (PO2), and forced expiratory volume in 1 second (FEV1) and higher serum IgG (p<0.05).*

58. Konstan MW, Butler SM, Wohl MEB, Stoddard M, et al. Growth and Nutritional Indexes in Early Life Predict Pulmonary Function in Cystic Fibrosis. J. of Pediatrics. June 2003: 624-630.—*This was an epidemiologic comparison of weight-for-age (WFA), height-for-age (HFA), percent ideal body weight (%IBW), and signs of lung disease at age 3 years with pulmonary function at age 6 years were assessed in 931 patients with CF. [Sample data were drawn form an ongoing epidemiologic study (Epidemiologic Study of Cystic Fibrosis) which has a 24,863 patient data-repository]. Poor growth indices were correlated with poor lung function at 3 and 6 years of age. This effect was greater with WFA and IBW than for HFA.*

59. Corey M, McLaughlin FJ, Williams M, Levison H. A Comparison of Survival, growth and Pulmonary Function in Patients with Cystic Fibrosis in Boston and Toronto. J Clin Epidemiol. 1988. 41(6): 583-591.—*This study compared growth outcomes and pulmonary*

function in two CF care centers; one in Toronto Canada ("liberal" dietary fat intake) and one in Boston, MA USA ("restrictive" dietary fat intake). Mean FEV1 in liters and percent predicted FEV1 were not different in Boston and Toronto patients. Boston patients tended to be shorter than Toronto patients. Median age of survival was 21 years in Boston and in 30 years in Toronto.

60. Wilschanski M, Rivlin J, Cohen S, Augarten A, et al. Clinical and Genetic Risk Factors for Cystic Fibrosis-related Liver Disease. Pediatrics 103:52-57, 1999.—*In 340 Israeli patients with CF, 80 patients had liver disease including 28 patients with histologic or sonographic evidence of cirrhosis. There was not association with specific CF-related mutations with presence or severity of liver disease. The discussion notes the association between CF-related EPI and liver disease and conjectures that CF with pancreatic sufficiency may correlate with non-liver disease (no data presented).*

61. Yankaskas JR, Marshall BC, Sufian B, Simon RH, et al. Cystic Fibrosis Adult Care. Chest 2004; 125: 1S-39S.—*This practice guideline discusses global treatment of patients with CF including patients with CF-related EPI. In summary from page 11S, "The decision to treat a patient with enzyme supplements rests on demonstrating the presence of steatorrhea. This generally correlates with symptoms of diarrhea, foul-smelling greasy stools, weight loss or poor weight gain, flatus and abdominal discomfort, and fat-soluble vitamin deficiency. For young adults who received diagnoses during childhood, enzyme supplementation should be continued. For newly diagnosed adults, a 72-h fecal fat collection should be performed while the patient is on a fixed oral fat intake or with dietary records." Also from page 11S "Fecal fat excretion of > 7% indicates steatorrhea in an adult and mandates the initiation of pancreatic enzyme and vitamin supplementation (see "Nutrition" subsection)." The nutrition subsection on page 13S advocate nutritional monitoring, particularly fat soluble vitamin (ADEK) assessments, and supplementation with 10,000 IU/day of vitamin A, 200 to 400 IU/day of vitamin E, 400 to 800 IU/day of vitamin D, and 2 ½ to 5 mg/week of vitamin K, with modification of these doses based on patients specific clinical factors; for example recent treatment with antibiotics.*

62. Consensus Conferences Concepts in CF Care. Volume X, Section I, March 28-29, 2001.—*This consensus document discusses global treatment of patients with CF including patients with CF-related EPI. The article advocates use of PEPs in patients with CF-related EPI, with EPI diagnosed symptomatically with confirmation by (1) duodenal intubation studies; (2) 72-hour fecal fat balance study; (3) immunoreactive trypsinogen; and (4) other markers such as fecal elastase-1 determination. This Reviewer notes that in clinical practice, intubation studies are impractical and there is reliance on symptomatology and stool fat studies such as CFA with lesser reliance on acid steatocrit.*

9.2 Labeling Recommendations

Labeling underwent extensive negotiations between the Applicant and FDA. See final negotiated labeling.

9.3 Advisory Committee Meeting

A meeting of the Pediatric Subcommittee of the Antiviral Drugs Advisory Committee (AVAC) was convened on 2-December-2008. Please refer to the final minutes of the AVAC for a summary of the information presented to the AVAC, questions presented to the AVAC, discussion by the AVAC, and final recommendations by the AVAC.

9.4 Additional Tables for the Pivotal Study

For illustrative purposes, each Pivotal Study patients' CFA (%) during Creon and Placebo treatment, change in CFA, mean Creon dose in Lu/gram dietary fat/day and Lu/kg/day, gender and age are shown in Table 26.

Table 26: CFA (%), Mean Lipase Dose, Age, and Gender for Patients in the Pivotal Study

Patient ID	Creon CFA	Placebo CFA	Change in CFA	Mean Dose Lu/Gram Dietary Fat/Day	Mean Dose Lu/Kg body weight/Day	Gender	Age (years)
0010-00001	92	47	45	3,482	11,707	F	28
0010-00002	90	41	49	3,871	11,470	M	25
0010-00003	90	32	59	4,004	9,990	M	26
0010-00004	90	40	50	3,752	8,487	F	22
0010-00005	82	23	59	3,728	13,132	F	13
0010-00006	96	55	40	4,579	14,059	F	38
0010-00007	96	91	5	4,244	10,561	M	21
0011-00001	93	67	27	5,492	13,241	M	19
0011-00002	93	42	51	4,874	10,924	M	27
0012-00001	84	23	61	4,452	8,685	F	14
0012-00002	98	38	60	4,041	7,462	M	28
0012-00003	88	43	45	3,910	8,103	M	28
0012-00004	97	72	24	4,048	7,701	F	17
0012-00006	82	67	16	3,800	8,479	M	19
0012-00007	89	43	46	3,359	9,258	M	12
0014-00002	94	41	53	4,440	6,338	M	43
0016-00002	88	58	30	4,510	8,873	F	15
0016-00003	72	43	29	4,610	17,270	M	17
0023-00001	78	51	27	2,996	11,157	M	22
0023-00002	84	77	7	1,405	6,644	F	18
0025-00001	81	51	30	3,999	13,902	M	30
0025-00002	95	68	27	4,350	9,982	M	28
0025-00003	96	32	64	5,077	12,019	F	23
0025-00004	87	64	23	5,121	11,704	M	29
0025-00006	78	83	-5	4,344	9,117	M	24
0025-00007	93	30	63	4,683	13,419	M	21
0027-00001	80	43	37	4,341	22,908	M	12
0027-00002	93	72	21	4,456	12,964	M	25
0028-00001	93	54	39	4,378	10,256	M	23
0028-00002	91	29	62	4,396	13,454	M	17
0031-00001	84	23	61	4,421	8,193	F	18

Source: This Reviewer's analysis.

Table 27 shows that 12 patients received ≥110% of the planned dose [4,000 Lu/gram dietary fat/day] (**bold** line), which is the maximum daily recommended dose when administering dose as Lu/gram dietary fat/day (also see section 7.6.4 of this review). The datasets indicate this was related to study design. Dose was given prior to meals, but some patients ate less food (fat) than provided which increased their daily dose.

Table 27: Pivotal Study, Mean (SD) Lu/Gram Dietary Fat/Day

ID	Mean		ID	Mean
0023-00002	1,405		0025-00002	4,350
0023-00001	2,996		0028-00001	4,378
0012-00007	3,359		0028-00002	4,385
0010-00001	3,482		0031-00001	4,421
0010-00005	3,728		0014-00002	4,440
0010-00004	3,752		0012-00001	4,452
0012-00006	3,800		0027-00002	4,456
0010-00002	3,871		0016-00002	4,510
0012-00003	3,910		0010-00006	4,579
0025-00001	3,999		0016-00003	4,610
0010-00003	4,004		0025-00007	4,683
0012-00002	4,041		0011-00002	4,874
0012-00004	4,048		0025-00003	5,077
0010-00007	4,244		0025-00004	5,121
0027-00001	4,341		0011-00001	5,492
0025-00006	4,344			

Patients below the bold line received ≥110% of the protocol specified dose (N=12). Source: This Reviewer's analysis

Tables 28 shows that 17 Pivotal Study patients received doses in excess of 10,000 Lu/kg/day (**bold** line). As noted in sections 5.3.1.5 and 7.6.4 of this review, the risk of fibrosing colonopathy increases with increasing daily lipase dose. The risk-benefit ratio with doses <10,000 Lu/kg/day [2,500 Lu/kg/meal] is considered favorable and doses above 24,000 Lu/kg/day [6,000 Lu/kg/meal] are associated with increased risk of fibrosing colonopathy and should not be used.

Table 28: Pivotal Study, Mean (SD) Lu/Kg/Day

ID	Mean		ID	Mean
0014-00002	5,983		0011-00002	11,255
0023-00002	6,644		0010-00002	11,505
0012-00002	7,523		0010-00001	11,951
0012-00004	7,672		0025-00003	12,019
0016-00002	7,711		0011-00001	12,935
0012-00003	8,006		0027-00002	12,964
0031-00001	8,332		0025-00007	13,035
0012-00006	8,479		0010-00005	13,132
0010-00004	8,487		0025-00004	13,556
0012-00001	8,643		0028-00002	13,599
0012-00007	9,258		0010-00006	14,059
0025-00006	9,487		0025-00001	14,459
0025-00002	9,982		0016-00003	14,571
0010-00003	9,990		0027-00001	22,908
0028-00001	10,202			
0010-00007	10,561			
0023-00001	11,125			

Source: This Reviewer's analysis

Table 29 shows all AEs reported in the Pivotal Study by incidence. AEs were more common during Placebo treatment and most AEs with either treatment were related to abdominal complaints frequently reported in patients with CF.

Table 29: All AEs Pivotal Study

System, Organ, Class	Preferred Term	Creon N=32	Placebo N=31
Congenital, familial and genetic disorders	Cystic fibrosis lung	0	1 (3)
Ear and labyrinth disorder	Tinnitus	1 (3)	0
Gastrointestinal disorders	Abdominal pain	3 (9)	8 (26)
	Flatulence	3 (9)	8 (26)
	Abnormal feces	1 (3)	6 (19)
	Constipation	1 (3)	0
	Duodenitis	1 (3)	0
	Feces discolored	1 (3)	0
	Gastritis	1 (3)	0
	Vomiting	1 (3)	1 (3)
	Abdominal pain upper	0	3 (10)
	Diarrhea	0	1 (3)
	Toothache	0	1 (3)
Injury, poisoning and procedural complications	Medication error	0	1 (3)
Investigations	Weight decreased	1 (3)	2 (6)
Metabolism and nutrition disorders	Hyperglycemia	1 (3)	0
	Hypoglycemia	0	1 (3)
Nervous system disorders	Dizziness	2 (6)	0
	Headache	2 (6)	8 (26)
Psychiatric disorders	Tearfulness	1 (3)	0
Reproductive system and breast disorders	Dysmenorrhea	1 (3)	0
Respiratory, thoracic and mediastinal disorders	Cough	2 (6)	0
	Epistaxis	1 (3)	0
	Pharyngolaryngeal pain	1 (3)	0
	Productive cough	1 (3)	0
	Wheezing	1 (3)	0
Skin and subcutaneous tissue disorders	Eczema	0	1 (3)
	Patients with Any AE	**16 (50)**	**22 (71)**

9.5 Discussion of Randomized, Blinded, Placebo-Controlled Studies of CMP

9.5.1 Introduction

A brief summary of 15 randomized, blinded, placebo-controlled studies of CMP is presented. Safety data from 14 of these studies was previously submitted; these data were reviewed as individual studies or as a component of prior ISS updates. The only new clinical information is from one study in adults with human immune deficiency virus (Study S245.3.119). The Applicant reports data quality/integrity issues with Study S245.3.119 preclude efficacy

assessments. This Reviewer is unable to determine if data from Study S245.3.119 are appropriate for safety assessments.

Since the majority of these data have undergone prior review (Ethan D. Hausman MD August 16-2007 and Fathia Gibril MD December 9, 2003), presentation is limited to a table summarizing study characteristics and a description of common AEs and SAEs.

9.5.2 Table of Studies

Table 30 lists controlled studies of the CMP and available study characteristics. This information was taken from the ISS dataset. Dose ranged from 955 to 7,651 Lu/kg/day. In four studies doses could not be verified. Treatment was from 1 to 16 weeks.

Table 30: Controlled Studies of CMP[1] (N=15 Studies)

Study	Disease[2]	Age in years	Estimated mean dose	N:n[3] and Duration in Days
S223.3.101	CF	12 to 18	7,651 Lu/kg/day	47:18 patients x 7 days
S223.3.102	CF	18 to 53	4,537 Lu/kg/day	50:18 patients x 6 days
Kreo 629*	CF	6 to 15	Unable to determine	11:11 patients x 12 days
223.2.01	CP	31 to 75	125,000 Lu/day (1,860 Lu/kg/day)	27:13 patients x 14 days
K245.5.005	CP	39 to 69	2,554 Lu/kg/day	40:17 patients x 14 days
S245.3.107	CP	44 to 66	Unable to determine	4:4 patients x 7 days
S245.3.115[4]	CP/PY	26 to 83	60,000 or 120,000 Lu/day (1,600 Lu/kg/day)	94:23 patients x 7 days CP 40 patients x 7 days PY
S245.3.112	DM	47 to 61	Unable to determine	6:3 patients x 7 days
S245.3.113	DM	36 to 73	Unable to determine	23:13 patients x 7 days
S245.3.110	DM	24 to 64	1,748 Lu/kg/day	80:39 patients x 112 days
S245.3.116	HIV	29 to 53	1,243 Lu/kg/day	10:6 patients x 28 days
S245.3.119[4]	HIV	18 to 57	2,604 Lu/kg/day	38:38 patients x 14 days
S248.4.001	AP	24 to 81	2,227 Lu/kg/day	56:27 patients x 28 days (26 to 30 days)
S248.4.002	AP	32 to 78	955 Lu/kg/day	21:10 patients x 84 days
S245.3.102	GY	47 to 79	4,567 Lu/kg/day	11:3 patients x 2 weeks

Source: This Reviewers analysis of the ISS dosing dataset.
[1]Randomized, double-blind, placebo-control except one (*) single blind study.
[2] CF=Cystic Fibrosis, CP=Chronic Pancreatitis, PY=Pancreatectomy, DM=Diabetes Mellitus, HIV=Human Immune Deficiency Virus, AP=Acute Pancreatitis. and GY=gastrectomy
[3]N:n=Randomized patients: patients receiving Placebo-Controlled CMP (excluding run-in periods)
[4] Substantive data quality or integrity issues reported by Applicant

9.5.3 SAEs and Common AEs in Blinded, Placebo-Controlled Studies of the CMP

The ISS update states 272 patients received either CMP or Placebo (271 CMP, 272 Placebo) under blinded, placebo-controlled conditions. Review of the ISS update and dose dataset indicates 284 patients received each treatment. This discrepancy is due to enrollment of several patients in more than one study. To avoid potential dilution of safety signals, this Reviewer will use the lower figures for the denominator for calculating SAE and common AE incidence.

SAEs were more common in Placebo- than CMP-treated patients (4% vs. 1%). Except for hypoglycemia related to absence of pancreatic endocrine mass (diabetes and pancreatectomy) which occurred in 3% of placebo-treated patients, no SAE was reported in >1% of any patient. SAEs reported more commonly in CMP than placebo-treated patients were atrial tachycardia, gastroesophageal reflux disease melena, pyrexia, metabolic encephalopathy, dyspnea, and lung disorder (<1% each). Review of the ISS update suggests these SAEs were related to underlying disease processes or other causes and did not appear to be related to CMP (Table 31).

Table 31: Incidence of SAEs from 15 Multi-Dose RBPC Trials of CMP; N (%)

System, organ, class	Preferred Term	CMP	Placebo
		N=271	N=272
Cardiac disorders	Atrial tachycardia	1 (<1)	0
	Acute myocardial infarction	0	1 (<1)
Gastrointestinal disorders	Gastroesophageal reflux disease	1 (<1)	0
	Impaired gastric emptying	1 (<1)	0
	Melena	0	1 (<1)
General disorders and administration site conditions	Pyrexia	1 (<1)	1 (<1)
	Heparin-induced thrombocytopenia	0	1 (<1)
	Edema	0	1 (<1)
Injury, poisoning and procedural complications	Injury	0	1 (<1)
	Subdural hematoma	0	1 (<1)
Metabolism and nutrition disorders	Hypoglycemia	0	3 (1)
Musculoskeletal and connective tissue disorders	Back pain	0	1 (<1)
	Neck pain	0	1 (<1)
Nervous system disorders	Metabolic encephalopathy	1 (<1)	0
	Dizziness	0	1 (<1)
	Hypoglycemic coma	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	Dyspnea	1 (<1)	0
	Lung disorder	1 (<1)	0
Skin and subcutaneous tissue disorders	Cold sweat	0	1 (<1)
	Any SAEs	**4 (1)**	**10 (4)**

In blinded, placebo-controlled trials of the CMP, the incidence of AEs was similar in CMP and placebo treated patients (71 to 72%). The most common AEs in CMP-treated patients were headache (13%), abdominal pain (9%), diarrhea and cough (7% each). The most common AEs in placebo-treated patients were abdominal pain, headache (12% each), diarrhea (11%), and vomiting (6%). In conclusion, the type of AEs was similar in CMP and placebo-treated patients (Table 32).

Table 32: AEs Occuring in ≥2% of Patients in Any Blinded Placebo Controlled Study of CMP (N=15 Studies)

System, Organ, Class	Preferred Term	CMP	Placebo
		N=271	N=272
Gastrointestinal disorders	Abdominal pain	24 (9)	32 (12)
	Diarrhea	20 (7)	30 (11)
	Constipation	16 (6)	8 (3)
	Nausea	15 (6)	15 (6)
	Vomiting	15 (6)	7 (3)
	Dyspepsia	14 (5)	11 (4)
	Abdominal pain upper	11 (4)	11 (4)
	Flatulence	10 (4)	15 (6)
	Abdominal distension	9 (3)	11 (4)
	Abdominal discomfort	5 (2)	3 (1)
General disorders and administration site conditions	Fatigue	11 (4)	5 (2)
	Pyrexia	8 (3)	7 (3)
	Malaise	6 (2)	6 (2)
Infections and infestations	Nasopharyngitis	11 (4)	9 (3)
	Influenza	7 (3)	7 (3)
Metabolism and nutrition disorders	Decreased appetite	7 (3)	2 (1)
	Hyperglycemia	7 (3)	6 (2)
Musculoskeletal and connective tissue disorders	Back pain	10 (4)	9 (3)
	Shoulder pain	5 (2)	6 (2)
Nervous system disorders	Headache	36 (13)	32 (12)
Respiratory, thoracic and mediastinal disorders	Cough	20 (7)	4 (1)
	Pharyngolaryngeal pain	11 (4)	5 (2)
	Lung disorder	8 (3)	0 (0)
	Productive cough	5 (2)	0 (0)
Skin and subcutaneous tissue disorders	Rash	5 (2)	3 (1)
	Any AEs	**192 (71)**	**195 (72)**

These findings suggest that most AEs were related to underlying disease and complications of underlying disease which is consistent with published literature and findings from the Pivotal Trial. This Reviewer concludes these findings do not substantially alter the safety profile of the TbMP or non-TbMP PEPs.

9.6 Additional Safety Information from Other Studies of CMP

New clinical data from 10 studies of the CMP were submitted in this CR. Clinical information from one study (S245.3.119) was included in information reviewed in section 9.5 of this review and a more complete description is provided in section 9.6.1 below.

Study characteristics of the remaining 9 studies are summarized in Table 3 in section 5.1 of this review. Of these remaining 9 studies, 3 studies were substantially complete and reviewed during the prior review cycle (Ethan D. Hausman, MD, August 16, 2007) and are summarized in section 9.6.2 below. The final completed study (S245.2.002) is summarized in section 9.6.3. Limited information available from 5 incomplete studies is summarized in section 9.6.4.

The studies are reviewed to inform the safety profile PEPs as a drug class and rather to address specific safety issues of the TbMP product formulation.

9.6.1 Study S245.3.119

This was a randomized, double-blind, placebo-controlled study of 38 patients with HIV associated weight-loss and steatorrhea, ages 18 to 57 years. Six females and 32 males were randomized. Treatment was placebo or CMP 225,000 lipase units per meal x three meals per day plus 25,000 to 50,000 lipase units per snack x 2 to 3 snacks per day for 2 weeks, followed by 2 weeks of the opposite treatment. The Applicant reports data integrity/data quality issues preclude efficacy assessments. Mean dose was 2,604 Lu/kg/day. A completed study report was submitted but individual datasets were not submitted. There were no deaths, withdrawals, or SAEs. AEs were reported in six patients. During CMP treatment there was one report each of acute pyelonephritis, diarrhea, and thrombocytopenia. During Placebo treatment there was one report each of acute bronchitis and headache. There was one report of hypokalemia in a patient during the follow-up period after completing placebo treatment.

A discussion of the thrombocytopenic event follows:

> Patient 02028, a 23-year old female in the Placebo→CMP group, experienced a platelet decrease from 226x10^9/L at Baseline to 34x10^9/L at Visit 3 and 29x10^9/L at Visit 4. The platelet decrease was documented on Day 1 of CMP treatment, and continued through the end of CMP treatment. The primary clinical laboratory data was not submitted and there is no way to determine if the thrombocytopenic specimens were clotted. This Reviewer concludes the relationship of thrombocytopenia to CMP can not be determined.

In summary, this Reviewer concludes the AEs reported during CMP treatment were similar to common complaints in the symptomatic-HIV patient population, untreated for EPI, and the AEs reported in the study are likely related to underlying disease rather than CMP. Thrombocytopenia is reported in patients with HIV-related bone marrow dysfunction and review of the Pivotal Study did not reveal clinically meaningful changes in platelet number. This Reviewer concludes these findings do not substantially alter the safety profile of the TbMP or non-TbMP PEPs.

9.6.2 Studies K245.5.703, S245.3.103, and S245.3.104

Studies K245.5.703 and S245.3.104 were open-label studies of CMP beginning with a five day placebo run-in. Study S245.3.103 was an extension study of the other two trials. One hundred eleven adult patients with chronic pancreatitis or pancreatectomy were screened

and enrolled into the lead-in studies, and 63 patients entered the extension study. Safety information was integrated into the ISS dataset. Individual study reports and datasets were not submitted. Substantial safety information from these studies was analyzed during the previous review (see Clinical Review, Ethan D. Hausman, MD; August 16, 2007).

There were no deaths. Six patients withdrew. The number of AEs in any patient at the time of withdrawal ranged from one to nine. The most common reasons for withdrawal were anorexia (3%) and abdominal pain (2%). There were 46 SAEs and the number of SAEs reported in any patient ranged from zero to nine. The most common SAEs were nausea, pyrexia, and vomiting (3%), anorexia, back pain, diarrhea, liver abscess, metastasis to liver, and recurrent pancreatic carcinoma (2% each). The case summaries were reviewed and this Reviewer concludes the SAEs appeared to be related to underlying disease and did not appear to be related to CMP treatment. This Reviewer concludes these findings do not substantially alter the safety profile of the TbMP or non-TbMP PEPs.

9.6.3 Study S245.2.002

This was a 3-day Placebo-run-in (wash-out), 53-week open-label uncontrolled study of the CMP in 5 patients with CF (3 male and two 2 female), ages six to 16 years. Mean dose was 5,943 Lu/kg/day. Safety information was integrated into the ISS dataset. Efficacy assessments for this CMP only trial are not performed in this review. There were no deaths or withdrawals. There were four SAEs.

> Patient 101202, a 16 year old male, experienced three SAEs. Appendicitis and pneumonia were reported during Placebo run-in, and pneumonia was reported four weeks later while on CMP treatment. CRFs are not available. This Reviewer concludes that these AEs were probably not related to CMP treatment.
>
> Patient, a 6 ½ year old male, experienced enuresis classified as an SAE in the follow up period. The patient recovered without treatment. CRFs are not available for review and PEP treatment, if any, during the follow-up period is unknown. This Reviewer concludes the relationship of this event to CMP is unlikely.

The most common AEs reported in this study were abdominal pain, cough, and pyrexia (60% each), and nasal congestion and stridor (40% each), which this Reviewer concludes reflects underlying pulmonary and gastrointestinal pathology in this patient group. This Reviewer concludes these findings do not substantially alter the safety profile of the TbMP or non-TbMP PEPs.

9.6.4 Incomplete Studies

Study S245.3.117 was an open-label, uncontrolled study of CMP in three patients with CF, at doses per investigator discretion. The safety data were previously reviewed as part of the 2006 ISS update (see Clinical Review, Ethan D. Hausman, MD; August 16, 2007). One patient was treated since the last safety update. One newly reported death was reported. Summary AE data were compared to data submitted during the prior review

cycle and this Reviewer agrees with the Applicant that no new clinically meaningful data were reported.

Studies S245.3.122, S245.3.123, S245.4.007, and S245.3.124 are partially completed studies of CMP employing a variety of blinding and control schemes. Completed study reports were not submitted. These studies do not employ placebo-control. No further comment is made regarding these studies.

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/s/

Ethan Hausman
4/30/2009 04:56:52 PM
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Joanna Ku
4/30/2009 05:53:44 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	20-725
Submission Code	AZ
Letter Date	17 November, 2006
Stamp Date	20 November, 2006
Original PDUFA Goal Date	20 May, 2007
Extended PDUFA Goal Date	18 August, 2007
Reviewer Name	Ethan D. Hausman, MD HFD-180
Through	Anne R. Pariser, MD Clinical Team Leader
Review Completion Date	16 August, 2007
Established Name	Pancrelipase Delayed-Release Capsules, USP
(Proposed) Trade Name	Creon® 6, 12, 24 capsules Minimicrospheres®
Therapeutic Class	Pancreatic Enzyme Product
Applicant	Solvay Pharmaceuticals, Inc
Priority Designation	Priority Review
Formulation	For oral administration
Dosing Regimen	Not to exceed 6,000 USP lipase units/kg/meal
Indication	Pancreatic insufficiency and steatorrhea
Intended Population	Patients with exocrine pancreatic insufficiency

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Abbreviations

The following non-standard abbreviations are used throughout this review:

CMP	Currently marketed product
TbMP	To-be-marketed product
MMS	Creon Minimicrospheres
MS	Creon Microspheres
PEP	Pancreatic Enzyme Product
PEI	Pancreatic exocrine insufficiency
CF	Cystic Fibrosis
CP	Chronic Pancreatitis
PY	Pancreatectomy
AP	Acute Pancreatitis
MedDRA	Medical Dictionary for Regulatory Activities
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
SOC	System Organ Class
PT	Preferred Term
ITT	Intent to treat population
PP	Per protocol population
R	Randomized
DB	Double blind
SB	Single blind
OL	Open label
PC	Placebo controlled
RW	Randomized withdrawal
CO	Cross over

EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This Reviewer recommends an Approvable (AE) action.

The safety and efficacy of the Creon MMS (CMP) have been established for the treatment of steatorrhea in patients with PEI, ages one month to adult. However, except for one bridging study, no clinical trials have been performed with the Creon to-be-marketed product (TbMP). The bridging study failed to establish the clinical comparability of the CMP and TbMP. Therefore, data in this CR are not adequate to support the approval of Creon TbMP.

One or more short term, efficacy and safety clinical trials with Creon TbMP are required to establish the safety and efficacy of the Creon TbMP. These studies are to be performed in patients with pancreatic exocrine insufficiency, such as cystic fibrosis. Efficacy in these clinical trials is to be demonstrated by a change in coefficient of stool fat absorption (CFA) from non-treatment or placebo treatment compared to CFA during treatment with the TbMP.

1.2 Recommendation on Postmarketing Actions

No post-marketing actions are warranted at this time.

1.2.1 Risk Management Activity

No risk management activities are warranted at this time.

1.2.2 Required Phase 4 Commitments

No phase 4 commitments are warranted at this time.

1.2.3 Other Phase 4 Requests

No other Phase 4 requests are warranted at this time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

1.3.1.1 Regulatory Background of Pancreatic Enzyme Products

Pancreatic Enzyme Products (PEPs) were first marketed prior to the Food Drug and Cosmetic Act of 1938 and continue to be available in the US as nutritional supplements and throughout the world as over-the-counter (OTC) and prescription therapies. In the 1990's concerns about potency and safety, including fibrosing colonopathy, led to a series of regulatory decisions establishing that PEPs were not generally recognized as safe and effective. It was determined that PEPs would be considered misbranded due to variations in potency. The Agency then declared its intent to consider all PEPs as new drugs requiring an approved new drug application (NDA) for continued marketing. This position was reaffirmed on 25 April 1995 with the publication of a Final Rule calling for all PEPs to be marketed drug products under approved NDAs by April 2008.

There is no currently available delayed release PEP approved for marketing in the US, though Creon and other PEPs are currently available as OTC nutritional supplements or prescription medicines in multiple other countries. The only previously approved PEP (Cotazym, approval December 1996) is not currently marketed in the US.

1.3.1.2 Overview of Clinical Program

Creon Pancrelipase Delayed-Release Capsules are classified as PEPs. PEPs contain a combination of lipases, amylases, and proteases, and are orally administered to patients with steatorrhea due to pancreatic enzyme insufficiency dues to a variety of primary disease processes, such as cystic fibrosis (CF).

In this Complete Response to a Not Approved action, the Sponsor submitted a request for approval of Creon® Minimicrospheres® (Creon MMS) for the indication for treatment of steatorrhea due to pancreatic exocrine insufficiency (PEI) associated with cystic fibrosis (CF) and chronic pancreatitis (CP). In support of this request, the Sponsor submits data from two new clinical trials of the CMP, an updated integrated summary of safety (ISS), including safety data from approximately 50 studies, 12 of which were not included in the original ISS, and data from a new bridging study conducted for the purpose of attempting to demonstrate the clinical comparability of Creon CMP with Creon TbMP.

This document reviews one new study of the CMP in adult patients with CP and PY (e.g., the New Adult PEI Study) and one new study in infants with CF (e.g., the New Infant CF Study), and the updated ISS, and contains summaries of clinical studies performed in CF and CP patients reviewed in the original NDA regulatory cycle (i.e., the Prior Pediatric CF, Prior Adult CF, and Prior Adult PEI studies). Selected information from other clinical studies is presented where noted.

Summary comments from other review disciplines are presented, including the Clinical Pharmacology review of the Bridging study (S245.2003), the Toxicology evaluation of the o-phthalic acid toxicology evaluation (study S0010.7.637X) and animal toxicology studies submitted under the Creon IND 47,546, the Division of Scientific Investigation (DSI) inspection report, the Chemistry, Manufacturing and Controls review, the Virology review, and the Microbiology review.

1.3.2 Efficacy

Two new short-term clinical efficacy and safety trials of Creon MMS (CMP) in patients with PEI were submitted in this CR amendment to the NDA and were reviewed for efficacy. Three short-term clinical efficacy and safety trials of Creon MMS (CMP) were submitted in the original NDA, and have been previously reviewed and summarized for efficacy during the original NDA review cycle. These five studies collectively enrolled 86 patients with CF, ranging in age from one month to 53 years, and 121 adult patients with PEI due to chronic pancreatitis (CP; n=62), and pancreatectomy (PY, n=59). The primary efficacy measure in these studies was coefficient of stool fat absorption (CFA) from non-treatment or placebo treatment compared with CFA during treatment with Creon MMS (CMP).

Efficacy results from studies are summarized below.

- New Infant CF Study (S248.3.003): In this short term, open-label study of 12 infants with CF, between one and 24 months of age, mean increase in CFA with Creon treatment compared to a no-treatment Baseline was 27% (95% C.I. 12.3, 41.1). Increase in CFA was greatest in four patients with non-treatment CFA less than 40%. Statistical inferences could not be made due to the small size of the study; however the clinical findings showed a clinically meaningful benefit of Creon treatment, and the magnitude of the results are similar to results seen in older pediatric and adult patients with CF. Thus, this study supports the clinical effectiveness of Creon CMP treatment of infants with PEI due to CF as young as one month of age.

- New Adult PEI Study (S245.3.115): In this short term, double-blind, placebo-controlled trial of low-dose and high-dose Creon MMS (CMP) in patients with PEI due to CP (N=35) and PY (N=59), mean increase in CFA for the ITT population (CP and PY) was 12% in patients receiving high-dose Creon MMS (CMP) compared to placebo (p-value 0.015). In the pancreatectomy sub-population, increase in CFA was approximately 18% in the high-dose Creon group compared to placebo (p-value 0.011). No significant difference in mean CFA compared to placebo was demonstrated in the low-dose Creon group (overall or by sub-population), or in CP patients treated with either low-dose or high-dose Creon CMP.

  The Sponsor performed an unplanned interim analysis during the study, and the potential effects on measure of statistical success were not provided. Therefore, no statistical inferences can be made for this study, and this Reviewer concludes that the results of the Adult PEI Study can not be used to support the efficacy of Creon CMP treatment for PEI due to CP or PY.

- Prior Pediatric CF Study (S223.3.101): In this short term, randomized, double-blind, placebo-controlled, treatment withdrawal trial of 38 children with CF, aged 7 through 17 years, CFA

was 31% higher (p-value < 0.001) in the Creon MMS (CMP) treatment group (N=18) compared to the placebo group (N=20). These findings show a statistically significant and clinically meaningful benefit of Creon treatment in pediatric patients with PEI due to CF, ages seven years and older.

- Prior Adult CF Study (S223.2.102): In this short term, randomized, double-blind, placebo-controlled, treatment withdrawal trial of 36 adults with CF, ages 18 through 53 years, CFA was 35% higher (p-value < 0.001) in the Creon MMS (CMP) treatment group (N=18) compared to the placebo group (N=18). These findings show a statistically significant and clinically meaningful benefit of Creon treatment in adult patients with PEI due to CF, ages eighteen and older.

- Prior Adult PEI Study (S223.2.01): In this short term, randomized, double-blind, placebo-controlled, treatment trial of 27 adults with CP, ages 38 through 74 years, CFA was 16% higher (p-value 0.0185) in the Creon MMS (CMP) treatment group (N=12) than the placebo group (N=14). These findings show a clinically meaningful benefit of Creon treatment in adult patients with PEI due to CP.

In conclusion, it is the overall assessment of this Reviewer that data from three short-term clinical efficacy and safety studies conducted in pediatric and adult patients with CF, and adult patients with CP support the effectiveness of Creon CMP treatment of steatorrhea in patients with PEI, and that Creon's effectiveness appears to be greatest in the most severely affected patients (i.e., patients with the lowest Baseline CFA). Results from the New Infant CF study were supportive of the clinical effectiveness of Creon CMP in the treatment of steatorrhea in infants with CF, ages one to 24 months these patients, and the results from this study were consistent with the results seen in clinical studies in older pediatric and adult patients. These findings support the labeling of Creon CMP for the treatment of steatorrhea in patients with PEI, ages one month to adult. The results from the New Adult PEI study cannot be used to support the effectiveness of Creon CMP in the treatment of PEI, due to problems with study conduct, and because of the results of the study were not clinically meaningful.

The Sponsor intends to market the Creon TbMP. However, no efficacy and safety clinical trials have been conducted to date with the Creon TbMP. The Bridging study that was submitted to the CR amendment, and was conducted for the purpose of demonstrating the comparability of the Creon CMP and TbMP products, failed to demonstrate the clinical comparability of the two products. Thus, the efficacy and safety results from studies with the Creon CMP cannot be used to support the clinical efficacy and safety of the Creon TbMP. Therefore, the efficacy (and safety) of the Creon TbMP for the treatment of steatorrhea in patients with PEI has not been demonstrated, and the information submitted in this CR amendment does not support the approval of Creon TbMP.

1.3.3 Safety

The Safety Update in this CR amendment contains information from 57 clinical studies conducted between July 1985 and May 2006, and performed with Creon MMS (CMP) or other formulations that are no longer marketed (e.g., Creon MS). Of the 57 studies in the ISS, 52 are multiple-dose studies

and five are single-dose studies. Safety information from 12 of the 57 studies is submitted for the first time in this CR amendment. Seven studies were not incorporated into the ISS due to data quality issues (e.g., inadequate methods for data collection, and incomplete safety datasets), and were not included in this safety review. Therefore, the ISS contains safety information from 50 studies.

Studies reported in the ISS include open-label, single- and double-blind, placebo-controlled, and uncontrolled trials, and contains information on 1,546 patients. Of 1,546 patients, 743 had CF, 358 had CP, 153 had pancreatic surgery, 109 had diabetes mellitus, 77 had acute pancreatitis, and 106 had other processes. Of 1,333 patients exposed to any Creon product, 991 received Creon MS (116 under double-blind conditions; Creon MS is not the CMP), and 594 received Creon MMS (232 under double blind conditions). Treatment exposure to Creon MMS ranged from six to 90 days (most common exposure was two to six weeks). Gender representation approximately 60% male and 40% female, and the age range of patients included in the Safety Update was from one month to more than 80 years of age.

The safety results are notable for the following:

Deaths

Eight death reports were included in the ISS and ten death reports were received from other sources (post-marketing and global safety surveillance reports). All deaths were attributable to underlying diseases, including recurrence/metastasis of carcinoma and pre-existing cardiovascular or cardiopulmonary disease. No deaths were attributable to Creon MMS (CMP). No pediatric deaths were reported. This Reviewer concludes that the deaths reported in the Complete Response were attributable to underlying disease and were not causally related to use of Creon MMS (CMP).

SAEs and Withdrawals

- In the ISS, SAEs were reported in 3.4% of patients receiving Creon MMS (CMP) and 3.4% of patients receiving placebo. The most common SAEs by System Organ Class (SOC) were gastrointestinal disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders. The most common SAEs by Preferred Term (PT) were pyrexia, cough, acute bronchitis, superinfection of the lung and hypoglycemia. In the opinion of this Reviewer, there was no clinically meaningful difference in incidence or type of SAEs between Creon MMS (CMP) and placebo treatment groups, and the SAEs reported were generally consistent with underlying disease.

- The most common SAEs in children with cystic fibrosis treated with Creon MMS (CMP) in the three pediatric CF safety studies included in the ISS were gastrointestinal disorders, and upper and lower respiratory tract infections. These SAEs appear to be consistent with underlying disease. An increased incidence of SAEs in children treated with Creon MMS (CMP) in these three studies was noted compared to patients treated with placebo (7% compared to 3%). The relevance of this finding is unclear, but may be explained by a greater exposure time of patients to Creon MMS (about 524 patient-weeks of exposure) than to placebo (about 60 patient-weeks of exposure).

- About 3% of patients in the ISS withdrew, including 2% of patients treated with Creon MMS and 3% in patients treated with placebo. The types of AEs leading to withdrawal were similar to the reported SAEs and commonly reported AEs, and appear to be related to underlying diseases and unrelated to administration of Creon MMS (CMP). An increased incidence of withdrawal was noted in patients with acute pancreatitis, which may be explained by the rapidly changing clinical state in patients with acute pancreatitis.

This Reviewer concludes that SAEs and withdrawals reported in the Safety Update were attributable to underlying disease, were expected in the patient populations under study, and did not appear to be causally related to use of Creon MMS (CMP).

Common Adverse Events

AEs were more common in patients treated with Creon MMS (61%) than in patients treated with placebo (49%). This disparity appears to be due to an increased incidence of less commonly reported AEs in the Creon MMS population, such as epistaxis and nasal congestion, than in patients treated with placebo. This disparity may also be due to differences in study designs for studies included in the ISS (e.g., open-label and lack of placebo control in many studies, which limited the placebo experience). However, the types and frequencies of the most commonly reported AEs in the ISS population are substantially similar between patients treated with Creon MMS (CMP) and patients treated with placebo, and include headaches, abdominal pain and other gastrointestinal complaints, respiratory disorders, and upper and lower respiratory tract infections. There were no obvious differences in the types of AEs reported by patients with different Baseline diagnoses or by age.

Special Safety Considerations with PEPs/Creon

Fibrosing colonopathy has been reported in children with Cystic Fibrosis treated with pancreatic enzyme products. No cases of fibrosing colonopathy (FC) were reported in the ISS, which is not unexpected due to the short duration of the studies and the relatively small safety population. One case of FC was reported in post-marketing reports, which was not definitively attributable to treatment with Creon MMS. Monitoring for FC is to be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products.

Hyperuricemia has been reported in patients with pancreatic exocrine insufficiency treated with PEPs. Though blood and urine uric acid monitoring were was not assessed in all studies in the ISS, hyperuricosuria was noted in several patients in the Prior Pediatric CF and Prior Adult CF Studies, all of whom had non-treatment blood uric acid levels near the upper limit of normal. Monitoring for hyperuricemia is to be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products.

In conclusion, in the opinion of this Reviewer, the safety of Creon MMS (CMP) has been adequately assessed. Withdrawals, SAEs, and non-serious AEs reflect findings reported in the original review of this NDA and in open source literature of patients with cystic fibrosis, and other causes of pancreatic exocrine insufficiency, and commonly include headaches, abdominal pain and other gastrointestinal

complaints, respiratory disorders, and upper and lower respiratory tract infections. AEs were most commonly attributable to underlying disease and appear unrelated to administration of Creon MMS (CMP). There were no new or notable safety findings with Creon administration reported in the Safety Update of the CR amendment to the NDA. In addition, all of the appropriate patient populations were studied in the Creon CMP clinical development program, including patients with cystic fibrosis as young as one month of age through adulthood, and patients with PEI due to other causes, such as CP.

Since the Bridging study failed to establish the comparability of the Creon CMP and TbMP, the safety results obtained with Creon CMP cannot be solely relied upon to demonstrate the safety of Creon TbMP, and at least one additional short-term safety (and efficacy) study with Creon TbMP will need to be performed to support the NDA approval of Creon TbMP.

1.3.4 Dosing Regimen and Administration

In order to optimize therapy while minimizing the risk of fibrosing colonopathy (FC), the Cystic Fibrosis Foundation (CFF), in conjunction with the FDA, recommends starting lipase doses according to age as described below.

The CFF recommends the following dose schedule for full meals:

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.
- Children ≤4 years old eating soft or solid foods: begin with 1,000 USP lipase units/kg/meal.
- Children >4 years old: begin with 500 lipase units/kg/meal.
- Doses in excess of 2,500 USP lipase units/kg/meal should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to significantly improve a documented low coefficient of fat absorption.
- The recommended per meal dose should be halved when ingesting snacks.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with fibrosing colonopathy.

Because safety and efficacy of the Creon TbMP have not been demonstrated in clinical trials, the final dose recommendations may change based on results of clinical trials of the TbMP; however, dosing recommendations for the TbMP should be consistent with current Cystic Fibrosis Foundation guidelines. The Sponsor's proposed dosing in the draft labeling for the CMP for pediatric patients is weight-based, and is generally consistent with the CFF guidelines.

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1.3.5 Drug-Drug Interactions

It is expected that patients with PEI may be exposed to prokinetic agents, H-blocking anti-histamines, and antacids. The efficacy studies included in the CR amendment allowed patients to be on these medicines if the dose was stable at the beginning and throughout study. In addition, many patients included in the studies in the CR amendment were on a large number and variety of medications for treatments of co-morbidities associated with underlying disease (e.g., antibiotics for infectious complications of CF). No reports of drug-drug interactions were noted in the CR amendment. Since Creon is not systemically absorbed, no interactions with systemically-active medications would be expected, although drug-drug interactions were not formally assessed as part of the Creon clinical development program.

1.3.6 Special Populations

The Creon clinical development program was conducted in patients where PEI is part of primary pathophysiology, including CF, CP, and PY, and in processes where PEI may present less commonly (e.g., diabetes mellitus). The clinical development program focused mainly on patients with CF, CP and PY.

Cystic fibrosis is an autosomal recessive disease estimated to occur in about 1 in 1,500 to 1 in 2,500 live births in the US, and affects an estimated 30,000 persons in the US. No cure exists but supportive treatment with anti-infectives, pancreatic enzyme supplements, and pulmonary, cardiac, and hepatic support has extended life expectancy out of childhood into the fourth and fifth decades. A majority of patients with CF have PEI, and CF patients account for about 42% of the population in the five key studies reviewed (New Infant CF, New Adult PEI, Prior Pediatric CF, Prior Adult CF, and Prior Adult CP Studies). The capacity to respond to treatment, demonstrated by increase in %CFA, appears to mirror severity of PEI, with more severely affected patients demonstrating greater response. This trend in response was seen in infants, youths, and adults with CF.

Studies in patients with cystic fibrosis included patients of both genders. The Sponsor provided information on children from one month of age through adulthood. The Sponsor provided safety information on children with cystic fibrosis less than seven years of age, and provided efficacy data on infants from one through 23 months of age. Adults with cystic fibrosis, from 18 to 53 years were also studied. Though the number of patients studied was small, males and females with CF appear to respond similarly. As expected, from epidemiological characteristics of cystic fibrosis, the CF population studied was predominantly Caucasian; therefore, there is insufficient information to determine any difference in response to treatment in CF patients based on ethnicity.

Pancreatectomy produces definitive and severe PEI. Pancreatectomy is a rare circumstance, offered as a component of treatment for certain gastric or pancreatic cancers, or as a result of trauma care. Patients with PY account for about 29% of the population in the five key studies. Similar to patients with CF, patients with more severe baseline disease demonstrated greater response.

In the opinion of this Reviewer, patients likely to be treated with Creon in the post-marketing setting, including the special populations noted above, have been adequately studied with Creon CMP in the Creon clinical development program.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The investigational agent studied in the application is Creon® Minimicrospheres® (MMS). Creon MMS is a delayed-release formulation of porcine-derived pancrelipase. Pancrelipase is derived from porcine pancreata, and contains varying amounts of lipases, amylases, and proteases, which break down lipids, carbohydrates, and proteins. Creon MMS was provided as gelatin capsules for oral administration. The Sponsor (Solvay) intends to market the product under the trade name Creon® 6, 12, and 24 capsules, which contain 6,000, 12,000, and 24,000 units of lipase, respectively.

Creon MMS is intended to provide an exogenous source of orally administered pancreatic enzymes to pediatric and adult patients with pancreatic exocrine insufficiency (PEI) from a variety of causes, such as Cystic Fibrosis (CF) and chronic pancreatitis (CP).

2.2 Currently Available Treatment for Indications

Pancreatic enzyme products (PEPs) have been marketed in the United States (US) without New Drug Applications (NDAs) since before the Federal Food, Drug and Cosmetic Act (The Act) of 1938. PEPs are currently widely available in the US as nutritional supplements produced and distributed by a number of manufacturers and sponsors. PEPs are available in enteric coated/delayed-release, and non-enteric coated formulations, which are not considered to be interchangeable.

One PEP (Cotazym) received NDA approval in December 1996, but is not currently marketed in the US. Thus, there is no pancreatic enzyme replacement therapy currently marketed in the US under an NDA.

2.3 Availability of Proposed Active Ingredient in the United States

Creon is currently commercially available in the US, but has not yet received approval under an NDA. Creon brand capsules first became commercially available in the US in 1987 as Creon Microsphere® (MS) capsules. In 1993, the Sponsor introduced the MMS form of Creon to replace the MS form. Currently, Creon MMS has marketing authorizations in approximately 70 countries worldwide.

Note: The Creon MMS formulation currently marketed in the US is referred to as the currently marketed product (CMP), and is a different formulation from the product formulation being proposed for NDA approval (the to-be-marketed product; TbMP).

2.4 Important Issues with Pharmacologically Related Products

PEPs were first marketed prior to The Act of 1938. Due to concerns about variability in potency, the Agency published a Notice of Proposed Rule making in the Federal Register (FR) on 15-July-1991 establishing that Over-the-Counter (OTC) PEPs are not considered generally recognized as safe and

effective (GRAS, and GRAE) products, and that OTC and prescription PEPs were considered misbranded due to variations in potency. Concurrently, the Agency declared its intention to consider all OTC and prescription PEPs to be new drugs requiring an approved NDA for continued marketing. This position was reaffirmed on 25-April-1995 with the publication of a Final Rule calling for all PEPs to be marketed drug products under approved NDAs in order to remain on the market. In April 2004, the Agency published in the FR a Notice of Requirement for NDA Approval of all PEPs within the next four years, with a deadline of 28-April-2008.

A single previously NDA approved PEP (Cotazym, approval December 1996) is not currently marketed in the US. Therefore, there is no currently available PEP approved for marketing in the US under an NDA, although Creon and other PEPs are expected to remain available as OTC products, nutritional supplements, or prescription medicines in the US until the 28-April-2008 deadline.

2.5 Presubmission Regulatory Activity

Creon is undergoing clinical investigation under Investigational New Drug Application (IND) 47,546. A summary of the regulatory history of Creon is as follows:

- Solvay Pharmaceutical Inc. (the Sponsor) originally submitted NDA 20-725 for Creon Microspheres (MS; pancrelipase delayed-release capsules) on 31-July-1997. On 24-September-1997, review of the NDA was suspended, and the Sponsor was placed on Application Integrity Policy (AIP) due to data integrity issues. The AIP was removed on 9-April-2003, and the review resumed under priority status.

- A Not Approved (NA) decision was rendered on 9-October-2003. Deficiencies noted in the NA letter from the Agency to the Sponsor included major CMC deficiencies, including a lack of drug product stability, inadequate characterization and specifications of drug substance and drug product, and incomplete viral safety evaluations. The letter additionally stated that once the CMC deficiencies were corrected, the Sponsor would need to link the intended to-be-marketed formulation (TbMP) with the formulation (CMP) used in the clinical trials. Methods to establish comparability of the CMP to TbMP were requested because the TbMP had not been investigated in Phase 3 clinical trials. Subsequent communications between the Sponsor and the Agency established that, in lieu of new clinical studies with the TbMP, comparability might be established by performance of a successful bridging study.

- The clinical reviewer (Fathia Gibril, M.D., M.H.Sc.), who performed the clinical review of the NDA at that time, concluded that clinical data supported the safety and efficacy of Creon MS; however, additional information was requested on children less than seven years old, who had not undergone evaluation in the Creon clinical development program.

The sponsor submitted a Complete Response (CR) to the Non-Approved decision on 20-November-2006, which is the subject of this review.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

CMC data have been extensively reviewed by the Product Reviewer (Wei Guo, Ph.D.), the Virology Reviewer (Ennan Guan, Ph.D.), and the Microbiology Reviewer (Anastasia Lolas, Ph.D.). Please see these reviews for more detailed information on the CMC data. Notable issues identified by these reviewers are briefly summarized as follows:

The Virology review (Ennan Guan, M.D., PhD) makes the following comments and recommendations:

- Manufacturing demonstrated effective inactivation of enveloped viruses, but not removal of viruses.
    - Therefore, it would be very useful if the firm can provide enveloped viral load by PCR-based test for their process intermediates to estimate the genomic equivalents.
- The Sponsor should set specifications for infectious PPV particles for the drug substance and final product, or set an action limit.

The CMC review (Wei Guo, Ph.D.) recommends an approvable (AE) action. The following specific review comments are provided:

- Adequate control of (b) (4) activity must be ensured in drug substance and product.
    - We recommend that the measurement of lipase potency in release and stability testing be performed in both the absence and presence of excess exogenous (b) (4)
    - Acceptance criteria for activity under each assay condition should be established and justified.

- The olive oil used as lipase substrate has an acceptance criterion of (b) (4) at (b) (4) of the total fatty acids, but testing results of nine batches have (b) (4) levels which vary from (b) (4)
    - Adjust the acceptance criteria of (b) (4) to reflect this fact to ensure that a consistent substrate is used in the lipase potency measurements.

- Dissolution testing of drug product should be performed on intact capsules.

- The acceptance criterion of the HPLC identity test used for drug substance and product are to be defined.

- The drug substance and product release test sampling plans are to be provided.

- The acceptance criterion of lipase activity for individual capsules tested was changed to (b) (4) of label claim on and after page 0151 of volume 1, submission dated March 21, 2007.

This is inconsistent with the proposed acceptance criteria of (b) (4) of label claim on pages 0118, 0127, 0131, 0134, and 0137 of the same submission.
    - Please address this inconsistency.

- Information on the manufacturer and specifications of container, closure, and seals for drug substance packaging is to be provided.

- Representative certificates of analysis of seals used in drug substance container/closure system are to be provided.

- Drug product labeling has been proposed as (b) (4)
    - Please specify the length of time excursions in temperature that are permitted.

The Microbiology review (Anastasia Lolas, Ph.D., 4-May-2007) recommends approval action. The following specific review comments were provided:

- (b) (4)
- *Salmonella* and *E.coli* limits, total aerobic microbial count, total combined yeast and mold counts, and post-approval stability protocols are acceptable.

3.2 Animal Pharmacology/Toxicology

Since extensive human experience exists with the PEPs, no non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA. Pharmacology/Toxicology studies submitted in this Complete Response (CR) submission were limited to evaluation of the excipient breakdown product, O-phthalic acid, conducted under and submitted to IND 47,546. Review of this information was conducted by the Animal Pharmacotoxicology Reviewer, David Joseph, Ph.D. (dated 8-June-2007). Please see the complete review of the non-clinical data for a detailed discussion of these findings.

In addition, a separate O-phthalic acid study report (S0010.7.637.X) was submitted in the NDA CR (volume 24 page 8,659). Notable issues identified by Pharmacology/Toxicology (per personal communications with Dr. Joseph on 14-June-2007) regarding the toxicology studies and the O-phthalic acid study report on 14-June-2007 are that "based on results of the submitted 4-week oral toxicity study of o-phthalic acid in dogs, the 2-year carcinogenicity studies of phthalic anhydride in rats and mice, and other preclinical studies of o-phthalic acid, p-phthalic acid, and phthalic anhydride, the estimated maximum dose of o-phthalic acid resulting from Creon® administration is not considered to be a safety concern."

Thus, there are no safety concerns identified with Creon from the review of the non-clinical data.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This application contains information from 57 clinical studies performed with Creon MMS, Creon MS, or both. Twelve studies are submitted for the first time in this CR submission. These 57 studies include all known studies conducted with Creon MMS. The studies were conducted between July, 1985 and May, 2006.

The clinical review of this application includes an assessment of clinical efficacy or outcomes measures from five Solvay-sponsored clinical studies. Two of these studies are reviewed for the first time in this document. Three of these studies were reviewed previously as part of the original NDA review for Creon (see Clinical Review by Dr. Gibril, dated 9-December-2003). These five efficacy studies include three short-term efficacy and safety studies of Creon in children and adults with Cystic Fibrosis (CF), and two short-term efficacy and safety studies in adults with chronic pancreatitis (CP) and pancreatectomy (PY). The remaining 52 trials could not be individually reviewed because of methodological deficiencies, including lack of controls, failure to study the CMP or TbMP, or lack of available study reports.

Note: A bridging study intended to compare lipase activity of the Creon CMP and TbMP preparations was performed in nine patients (see comments in the Clinical Pharmacology section of this review [Section 5], and the Biopharmacology review by Tien Mien Chen, Ph.D.). Except for the bridging study, all studies were performed with the Creon CMP. No clinical efficacy and safety studies have been performed to date with the Creon TbMP.

Safety information is provided from 57 studies. Twelve of these 57 studies are submitted for the first time with this CR. Of the 57 studies, datasets and study reports for seven studies were not provided due to data quality issues (not further clarified by the Sponsor). Therefore, the Integrated Summary of Safety (ISS) contains information from 50 studies. Additional safety data from European post-marketing reports of the MS and MMS products is also provided for review. A number of these 57 studies could not be individually reviewed because of methodological deficiencies, including lack of controls, failure to study the CMP or TbMP, and lack of available study reports.

4.2 Tables of Clinical Studies

The clinical studies reviewed or summarized in this Clinical Review are summarized in Table 1 below. These studies include one new trial of Creon MMS (CMP) in infants with CF and one new trial of CMP in adults with PEI due to chronic pancreatitis (CP) or pancreatectomy (PY), which are submitted for the first time in the Complete Response, and the two CF trials and one CP trial that were previously reviewed during the original submission of this NDA. Safety information from three trials of Creon MMS and Creon MS in children with CF included in the ISS is summarized; however review of these three trials for efficacy was not possible due to missing study reports and a lack of uniform

treatment (drug and placebo) across the three studies (a table of all clinical studies conducted with Creon MMS and Creon MS is located in Appendix section 10.2).

Table 1: List of Studies Individually Reviewed or Summarized in this Clinical Review

Study	Design	Patient Population
S248.3003 New Infant CF Study	Eight-week, open-label (OL), efficacy and safety study. Efficacy was evaluated by comparing a no-treatment baseline CFA to CFA on Creon treatment.	Infants with CF, 1 to 24 months old N=12
S245.3.115 New Adult PEI Study	Two-week, randomized (R), double-blind (DB), placebo-controlled (PC), parallel-group, efficacy and safety study of Creon (1.5 or 3.0 g/day) vs. placebo. Efficacy was evaluated by comparing a no-treatment baseline CFA to CFA after seven days of treatment.	Adults with CP and PY, 26 to 83 years N=94
S223.3.101 Prior Pediatric CF Study	Three- to six-week, DB, PC, randomized-withdrawal (RW), efficacy and safety study. All patients were treated with OL Creon upon enrollment (titrated to clinical effect), then randomized to DB Creon vs. placebo treatment. Efficacy was evaluated by comparing baseline CFA (on-treatment) to CFA in DB, RW period (while receiving Creon or placebo).	Children with CF, ages 7 to 17 years N= 38
S223.3.102 Prior Adult CF Study	Three- to six-week, DB, PC, RW efficacy and safety study of same design as Study S223.3.101 (Pediatric CF Study).	Adults with CF, 18 to 53 years N= 36
223.201 Prior Adult CP Study	Two-week, R, DB, PC, efficacy and safety study. Efficacy was evaluated by comparison of mean CFA of placebo and Creon treatment groups during the DB phase of the study.	Adults with CP, 38 to 74 years N= 27
S245.3118 Prior Infant CF Safety Study	Six-week, R, OL, cross-over (CO) study in infants with CF, which compared Creon MMS to Creon MS. Endpoint was caregiver preference of MMS vs. MS. All patients received open-label placebo for 1-2 weeks in order to establish Baseline CFA. All patients were randomized to receive either two weeks of Creon MMS followed by two weeks of Creon MS, or two weeks of Creon MS followed by two weeks of Creon MMS (OL treatment period). There was no placebo control group during the OL Treatment period..	Children with CF, ages 6 to 36 months N=40
S245.3105 Prior Pediatric CF Safety Study	Ten-week R, OL, CO study that compared efficacy and safety of Creon 10,000 MMS to Creon 8,000 MS. After a two-week run-in period with Creon 8,000, patients were randomized to receive either two weeks of Creon MMS followed by two weeks of Creon MS, or two weeks of Creon MS followed by two weeks of Creon MMS.	Children with CF, ages 3 to 17 years N=60 (60 patients received MS, 58 patients received MMS)
K245.5004 Prior Young Adult CF Safety Study	Six-week R, DB, CO study of efficacy of Creon MMS compared to Creon MS. After two to three weeks of placebo wash-out, patients were randomized to receive either two weeks of Creon MMS followed by two weeks of Creon MS, or two weeks of Creon MS followed by two weeks of Creon MMS. There was no non-treatment or placebo phase from which to establish Baseline CFA. There was no placebo control group during treatment with MMS or MS. The endpoint was comparison of mean CFA between MMS and MS treatment periods.	Patients with CF, ages 4 to 31 years N=34

4.3 Review Strategy

The most important new studies submitted to this application were the New Infant CF study (S248.3003) and the New Adult PEI study (S245.3.115). The comprehensive short-term efficacy and safety data submitted to the application for these two studies permitted substantive clinical review.

The New Infant CF study is an eight-week, open-label, uncontrolled, non-randomized, short-term efficacy and safety study of 12 infants, ages one to 24 months old, with PEI due to CF. The primary efficacy endpoint was the difference between the baseline (no-treatment) coefficient of fat absorption (CFA) compared to CFA after two weeks of Creon CMP treatment. Safety was assessed during eight weeks of Creon treatment. This study showed a clinically meaningful increase in CFA with treatment compared to no-treatment.

The New Adult PEI study is a 13-day, randomized, double-blind (DB), placebo-controlled, short-term efficacy and safety study of 94 adult patients with PEI due to chronic pancreatitis (N=35) or pancreatectomy (N=59). Efficacy endpoints were assessed after one to two weeks of DB treatment (with Creon or placebo) compared to the five-day baseline (placebo treatment) period. Safety data were collected from screening through completion of the eighth day of DB treatment. This study showed a trend toward increased CFA from baseline (no treatment) compared to CFA while on Creon treatment in the DB period.

Efficacy and safety analyses of the New Infant CF and New Adult PEI studies are emphasized in this review, and comprehensive reviews of these studies are summarized in the Appendix section under Individual Study Reports. Summaries of efficacy and safety studies (Prior Pediatric CF, Prior Adult CF, and Prior Adult CP studies) reviewed as part of the original NDA review for Creon (from Dr. Gibril's review) are also included in the Integrated Review of Efficacy section (section 6) of this review, as these studies demonstrated the efficacy of Creon CMP in the treatment of PEI.

As noted in section 4.1 of this review, substantive review of efficacy outcomes for the remaining 52 studies could not be performed due to methodological issues, including lack of adequate controls or lack of study of the MMS form of the drug. Therefore, no other studies are reviewed for efficacy.

Comprehensive individual safety reviews of the New Infant CF and New Adult PEI studies and a comprehensive safety review of the ISS were performed by this Reviewer. Review of the Prior Infant Safety, Prior Pediatric Safety, and Prior Young Adult CF Safety Studies was limited to an assessment of the Adverse Events (AEs) reported for these studies, which are summarized in the Integrated Review of Safety section (section 7) of this review. Lack of adequate controls in these three studies precluded substantive evaluation of efficacy.

4.4 Data Quality and Integrity

Data problems encountered with this application were noted during the review cycle that resulted in multiple information requests (IRs) being submitted to the Sponsor. These IRs included requests for the submission of incomplete data elements needed to complete the safety analysis. Responses from the Sponsor were sufficient to permit an evaluation of the safety data, with the exception of 1,198

adverse events from 12 studies that were not classified for seriousness or severity. Please see sections 7.1 and 7.1.5.2 of this review for a complete discussion of the issues concerning AE datasets ADVERSE, ADV, and EXTADV.

The Division of Scientific Investigation (DSI) performed one clinical site audit for this application, including inspection of the clinical site that conducted the bioequivalence/bridging study located in Marseilles, France. The overall observations noted by the DSI Inspector (Michael F. Skelly, Ph.D.) were that "The inspection could not confirm the identity of the pancrelipase products dosed to patients on each occasion. The analytical method validations and quality control programs failed to demonstrate the performance of the analytical methods before and during the study. All of the normalized study endpoints are compromised by the lack of raw data for the PEG 4000 method validation, calibration, and quality control." Thus, the overall conclusion from this inspection is that this study was not reliable as performed, and cannot be used to provide evidence of bioequivalence between the Creon CMP and TbMP.

4.5 Compliance with Good Clinical Practices

The Sponsor states that the Infant CF study and the Adult PEI study were carried out in accordance with Good Clinical Practice (GCP) regulations. The three studies reviewed during the original submission of this NDA were also reported to have been performed according to GCP regulations.

Formal assessment of GCP adherence in the older studies could not be performed. However, most of the remaining older studies submitted for review were not essential to the evaluation of the efficacy and safety of Creon. These older studies were not reviewed for efficacy, and safety information from these older studies was reviewed only as supportive evidence as part of the review of the ISS. These older studies could not be individually reviewed because of methodological deficiencies, including lack of controls, failure to study the CMP or TbMP, and lack of available study reports.

4.6 Financial Disclosures

Financial disclosure forms were reviewed for the New Infant CF study (S248.3.003), the New Adult PEI study (S245.3.115), and the Bridging study (S245.2.003). No financial interests were disclosed by any of the Investigators who participated in these studies.

Since the three efficacy studies previously reviewed in the original NDA submission (Prior Pediatric CF Study, Prior Adult CF Study, and Prior Adult CP Studies) were completed prior to 2-February-1999, disclosure of financial interest was not required. (The Agency published the Final Rule on Financial Disclosures by Clinical Investigators in the Federal Register on 31-December-1998 (21 CFR Part 54, Docket No. 93N-0445). As of 2-February-1999, compliance with disclosure of information regarding significant payments was made that applies to studies pertaining to a drug submitted for a marketing application where the study in question 1) shows that a product is effective; 2) shows equivalence to an effective product; 3) or makes a significant contribution to evidence of safety for studies ongoing as of 2-February-1999.)

5 CLINICAL PHARMACOLOGY

The clinical pharmacology data in this submission includes information from a single bioequivalence/bridging (Bridging) study (S245.2.003), titled "Cross-over pharmacology study to compare the duodenal lipase activity of two Creon® formulations in duodenal aspirates in patients with pancreatic exocrine insufficiency due to chronic pancreatitis." These data have been extensively reviewed by the Clinical Pharmacology Reviewer (Tien-Mien Chen, Ph.D.); please see the Clinical Pharmacology Review for the complete review of these data. The Bridging study was conducted for the purpose of demonstrating the comparability of the CMP and the TbMP, as all clinical efficacy studies were conducted with the CMP, and no clinical efficacy (and safety) studies to date have been conducted with the TbMP.

The Bridging study was a double-blind, randomized, single-center, 2X2 crossover, duodenal intubation study conducted in 15 adult patients with chronic pancreatitis. Each patient underwent an overnight fast, then received a meal with a dose of Creon CMP or TbMP (containing 60,000 units of lipase), and then underwent continuous duodenal aspiration collections over a three-hour period. Overall pancreatic lipase activity was determined from the aspiration specimens. Nine patients completed both phases of the study. Dr. Chen's findings for the Bridging study are briefly summarized as follows:

- The results showed that there was high inter-subject variability observed for both formulations.
    - Ten results showed that the individual values were higher than the administered dose of 60,000 units of lipase (almost four-fold the administered dose).
    - Conversely, two patients had no or little lipase activity measured in their duodenal aspiration samples.
- These observations rendered the study unreliable as a tool to establish comparability between the two formulations.
- The overall conclusion of the Clinical Pharmacology Reviewer from the data submitted in this study is that the Sponsor has not demonstrated that the TbMP is comparable to the CMP.

Thus, the comparability of the CMP with the TbMP could not be established by the Bridging study.

5.1 Pharmacokinetics

PEPs act locally in the gastrointestinal (GI) tract and are not absorbed; therefore, pharmacokinetic studies are not applicable.

Pharmacokinetic and pharmacotoxicology studies of the excipient breakdown product O-phthalic acid present in Creon tablets were performed in animal models and submitted for review under IND 47,546, and a separate pharmacokinetic summary as study report S0010.7.637.X was submitted to the NDA CR (volume 24 page 8,659). This information has been extensively reviewed by the

Pharmacotoxicology Reviewer (David Joseph, Ph.D.). Dr. Joseph's conclusions are summarized as follows:

There is no substantial risk from chronic phthalate exposures at expected daily doses of Creon, and the estimated maximum dose of O-phthalic acid resulting from Creon administration is not considered to be a safety concern.

5.2 Pharmacodynamics

Lipase, amylase, and protease act locally in the GI tract and are not systemically absorbed; therefore, pharmacodynamic studies are not applicable.

5.3 Exposure-Response Relationships

Traditionally, individual patient dosages of PEPs are determined by titration of the dose to clinical response (i.e., decreased steatorrhea/diarrhea). No formal dose-response studies were performed in support of the Creon clinical development program; however, two dosing groups were compared to placebo and against each other in the new Adult PEI Study. Please refer to the clinical review of the new Adult PEI study in Appendix section 10.1.2.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Sponsor is proposing that Creon MMS (TbMP) receive the following indication:

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

The data submitted to the Creon application is not supportive of this indication, as no efficacy studies have been conducted with the TbMP, and the Bridging study failed to establish comparability between the CMP and the TbMP. Therefore, no evidence of clinical efficacy currently exists for the Creon TbMP.

6.1.1 Methods

This Complete Response submission includes clinical efficacy measures from five short-term efficacy and safety clinical trials, two of which are newly submitted for review (Infant CF study and Adult PEI study). Supplemental efficacy information was available for review from 52 additional studies; however, the predominantly open-label and uncontrolled nature of these studies did not permit substantive review of efficacy data. Therefore, these 52 studies were not analyzed for efficacy by this Reviewer for this clinical review.

The clinical development program focused on the treatment of patients with PEI due to CF, CP, and PY. The comprehensive efficacy and safety data from the New Infant CF study and the New Adult PEI study permitted substantive review in 12 infants with CF and 94 adults with PEI due to CP (N=35) and PY (N=59), respectively. The data submitted from these studies were analyzed for the purpose of making a determination of the short-term effectiveness and safety of Creon in these patient populations. Primary and secondary efficacy endpoints and safety findings for these two trials are presented (secondary efficacy endpoints are presented only where noted). Secondary endpoints which are components of primary endpoints are not reviewed independently. The FDA Statistical Reviewer, Sonia Castillo, Ph.D., also reviewed these two efficacy studies, and conducted analyses on the primary efficacy endpoints. The findings from Dr. Castillo's review are summarized in this review.

In addition, the results for the three studies that were reviewed for safety and efficacy as part of the original NDA review for Creon were summarized (from Dr. Gibril's review) in this clinical review; however, since these studies were previously reviewed in detail, this Reviewer did not repeat the review of these studies. Instead, summaries of primary efficacy endpoints and safety findings for these three efficacy trials are presented as these studies were assessed by Dr. Gibril as having demonstrated the efficacy of Creon CMP in the treatment of PEI. Please refer to the clinical review from the original submission (Dr. Fathia Gibril, 9 December 2003) for a full discussion of the three previously reviewed efficacy trials.

Note: All of the clinical studies included in this review (with the exception of the Bridging study discussed above in section 5 Clinical Pharmacology) were conducted with the Creon CMP product. No clinical efficacy and safety studies have been performed to date with the Creon TbMP.

6.1.2 General Discussion of Endpoints

Pancreatic exocrine insufficiency (PEI) is a feature of multiple diseases, including CF and loss of functional exocrine mass (e.g., due to pancreatectomy or chronic pancreatitis). Clinical features of PEI are fat, protein, and carbohydrate malabsorption and malnutrition, and primary laboratory features include decreased blood fat soluble vitamins, increased stool fat content, and decreased CFA.

As described in published consensus documents (e.g., Borowitz, DS, Grand, RJ; Durie, PR., J Pediatrics, Nov 1995),[1] decreased CFA is an accepted indicator of PEI, and an increase in CFA is associated with enhanced pediatric growth and development.[2] A clinically meaningful increase in CFA in CF patients is accepted to be an increase of 30% or greater in the most severely affected patients (i.e., those patients who have baseline CFA less than 40%). There is no accepted clinically meaningful increase in CFA that has been determined for patients with PEI due to causes other than CF; however, as PEI due to any cause has similar clinical findings, it would be reasonable to consider this degree of change as meaningful in PEI due to PY and CP. In addition, there is no accepted change in CFA that has been shown to be clinically meaningful in patients with a Baseline CFA greater than 40%. Patients with higher CFAs at Baseline tend to have smaller increases in CFA with PEP administration, as these patients have a lesser capacity to respond. Therefore, and in concert with the Agency's "Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products –Submitting NDAs",[3] the Division accepts the use of CFA as the primary efficacy measure in the clinical studies conducted in the Creon clinical development program as reasonable and appropriate. Since it is

expected that the magnitude of change in patients' CFA with PEP administration would depend upon the Baseline (no treatment) CFA, the Division would expect to see larger increases in percent CFA (approaching 30%) in patients with the lowest Baseline CFAs (e.g., <40%), and lesser increases in CFA in patients with higher baseline CFA (e.g., >40% to <80 %).

In the five clinical studies reviewed for efficacy as part of this Clinical Review, CFA was assessed in the following manner:

Meals with pre-specified fat composition were provided, and prepared diets were consumed for five days. After completion of the second day of prepared meals, all stools produced over a 72-hour period (days three through five of prepared meal consumption) were collected. The percent CFA (%CFA) was determined using the following formula:

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

Change in CFA was measured in one or both of two ways: 1) mean change between non-treatment and treatment period; and/or 2) comparison of mean change between placebo and treatment groups compared to each group's non-treatment baseline.

In the New Infant CF study, patients were eligible for enrollment in the study if they had a Baseline CFA less than or equal to 70%, and successful treatment was defined as a treatment period CFA 90% or greater. Secondary outcome measures in the Infant CF study included change in number of stools per day, weight for height, and change in body mass index. These secondary endpoints are reviewed; however, they are of lesser importance given the short-term nature of this study, and were not felt to be substantively important to the determination of efficacy. Presentation and discussion of these secondary endpoints is found in Appendix 10.1.1 of this review.

In the New Adult PEI study, patients were eligible for enrollment in the study if the had a Baseline CFA no greater than 80%. Primary efficacy outcome was change of %CFA during the placebo period compared with change in %CFA during treatment. A definition for success for change in %CFA in this study was not provided. Secondary endpoints for this study included change in number of stools per day and change in daily caloric intake. These secondary endpoints are reviewed; however, they are of lesser importance given the short-term nature of this study, and were not felt to be substantively important to the determination of efficacy. Presentation and discussion of these secondary endpoints is found in Appendix 10.1.2 of this review.

The Sponsor also collected information on treatment-associated changes in daily dietary fat intake, and stool fat content. Dietary fat intake and stool fat content are both components of %CFA and are not independently reviewed.

6.1.3 Study Design

The two new clinical studies submitted to this application are reviewed in detail by this Reviewer: the New Infant CF study and the New Adult PEI study. The reader is directed to the individual study reports located in appendices 10.1.1 and 10.1.2, respectively, for a more detailed discussion of these studies. Additionally, summary information on the three previously reviewed trials (i.e., the Prior Pediatric CF, Prior Adult CF, and Prior Adult CP studies) is presented. New and independent reviews of these prior studies were not performed by this Reviewer.

6.1.3.1 New Infant CF Study (Study S248.3003)

6.1.3.1.1 Design, Treatment, and Population

The New Infant CF study was an eight-week, open-label, single-arm, efficacy and safety study of twelve infants with CF, age one through 24 months. Twelve infants (5 male [M], 7 female [F]) were enrolled, including five treatment naïve children, and seven children with previous exposure to PEPs (the duration of prior exposure to PEPs was three weeks to 21 months). All children underwent a no-treatment period of seven to ten days (minimum six days), which served as a wash-out period for children with prior exposure. Baseline CFA was performed after at least 72 hours of no-treatment. All children were then treated with Creon MMS for eight weeks. The daily dose was 2,000 lipase units per gram of fat intake. The study report did not indicate a maximum allowable daily dose.

6.1.3.1.2 Objectives and Outcomes Measures

The primary objectives of the study were the evaluation of efficacy after two weeks of treatment with Creon, and the evaluation of safety after two, five, and eight weeks of treatment. Efficacy was evaluated by changes from Baseline after two weeks of treatment in CFA, stool characteristics, growth indices, and laboratory evaluation of nutritional parameters. Safety was evaluated by changes from Baseline in medical history, physical examinations, and safety laboratory analyses (e.g., chemistry panel and hematology), and the occurrence during treatment of adverse events.

6.1.3.1.3 Patient Eligibility/Inclusion and Exclusion Criteria

Patients were eligible for study participation if they were ages one through 24 months, and had:

- A diagnosis of CF by two sweat tests or by gene analysis;
- PEI defined by age-adjusted steatorrhea with age-adjusted criteria, including:
    - <4 months of age: >4 g fecal fat/24 hr,
    - 4 to 12 months: >3 g/24 hr,
    - >12 months: >3-4 g/24 hr,
    - or stool chymotrypsin <5 U/g stool; and
- Baseline CFA <70% at end of no-treatment wash-out period.

Children were excluded from study participation for any known illness judged to put them at risk for participation in the study, including meconium ileus or pre-existing pulmonary disease, or known

allergy to porcine pancreatic products, or any other concomitant PEP exposure during the washout period.

6.1.3.1.4 Concomitant and Prohibited Medications

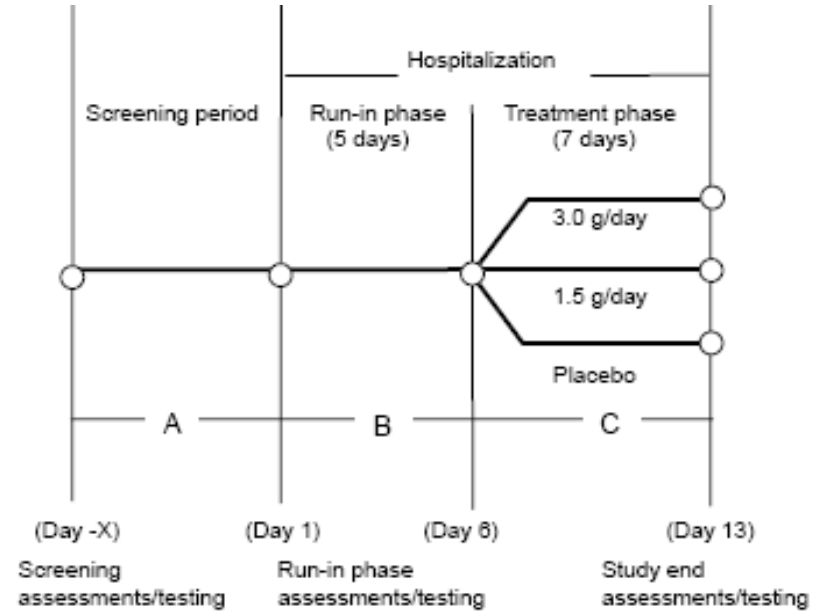
Concomitant use of other PEPs was not allowed from the beginning of the washout period through completion of the study. Use of proton pump inhibitors (PPIs), antacids, and H2-receptor blocking antihistamines, and prokinetic agents were permitted for use during the study only if they were in use at the time of enrollment. Patients who were not treated with (PPIs), antacids, and H2-receptor blocking antihistamines, and prokinetic agents were not allowed to take them during the whole study period (e.g., enrollment through final safety assessment). There is no comment in the protocol regarding whether dose changes of the preceding medicines were allowed during the study period. Medications not thought to interfere with the investigational agent were allowed. Doses and dates of use of concomitant medications were recorded in the CRFs.

6.1.3.2 New Adult PEI Study (Study S245.3.115)

6.1.3.2.1 Design, Treatment, and Population

The New Adult PEI study was a 13-day, randomized, double-blind, parallel-group, multi-center study to determine the efficacy and safety of SA-001 (Creon MMS) in adults with PEI due to chronic pancreatitis (CP, N=35) or pancreatectomy (PY, N=59). On completion of screening, patients underwent five days of single-blind placebo treatment to establish a Baseline CFA. Only patients with Baseline %CFA less than 80% were randomized to receive seven days of double-blind (DB) treatment with either placebo, Creon 1.5 gram/day (60,000 lipase U/day), or Creon 3.0 gram/day (120,000 lipase U/day). Efficacy was evaluated by the comparing mean change in CFA from baseline (placebo treatment) to CFA after seven days of DB treatment (i.e., placebo, 1.5 gram/day, and 3.0 gram/day). The overall study design is presented in Figure 1 below (electronically reproduced from the Sponsor's submission, volume 48, page 17,528).

Figure 1: New Adult PEI Study (S245.3.115), Study Phases



A: the screening period after obtaining informed consent until the study start
B: the 5-day placebo administration phase
C: the 7-day treatment phase with SA-001 3.0 g/day, 1.5 g/day, or placebo

6.1.3.2.2 Objectives and Outcomes Measures

The primary objectives of the study were the assessment of efficacy and safety. Efficacy was evaluated by comparing Baseline (placebo) CFA to CFA after seven days of DB treatment. Other efficacy parameters included change from Baseline in stool characteristics, and laboratory evaluation of nutritional parameters. Safety assessments included change from Baseline in history, physical examination, and laboratory assessments, and the occurrence during DB treatment of adverse events.

A secondary objective was to determine any difference between change in CFA between the low-dose and high-dose treatment groups.

6.1.3.2.3 Patient Eligibility/Inclusion and Exclusion Criteria

Patients were eligible for study participation if they were at least 20 years old, and had a diagnosis of either CP or PY with at least 7.5 g/day of stool fat at screening. Prior treatment with PEPs was allowed, but treatment must have ended no later than immediately prior to the beginning of the five-day placebo run-in phase.

Patients were excluded from study participation if their pre-study diet did not consist of at least 40 gram/day of dietary fat; if there was known clinically significant cardiovascular, gastrointestinal (other than primary disease), urogenital, or psychiatric/neurological disease; known allergy to the study drug or similar drug products; acute pancreatitis; superimposed acute pancreatitis, or if pregnant or lactating.

6.1.3.2.4 Concomitant and Prohibited Medications

Concomitant use of other PEPs was not allowed from the beginning of the placebo run-in phase through completion of the study. Use of proton pump inhibitors (PPIs), prokinetic agents, antacids, and H2-receptor blocking antihistamines were permitted for use during the study if they were in use at the time of screening, and the dose remained constant throughout the study.

6.1.3.3 Summaries of Clinical Trials Previously Reviewed: Prior Pediatric CF Study (S223.2.101), Prior Adult CF Study (S223.102), and Prior Adult CP Study (223.2.01)

Three short-term efficacy and safety studies were previously reviewed as part of the original NDA submission for Creon, and only brief summaries from the original clinical reviews are provided here.

6.1.3.3.1 Prior Pediatric CF Study (S223.2.101)

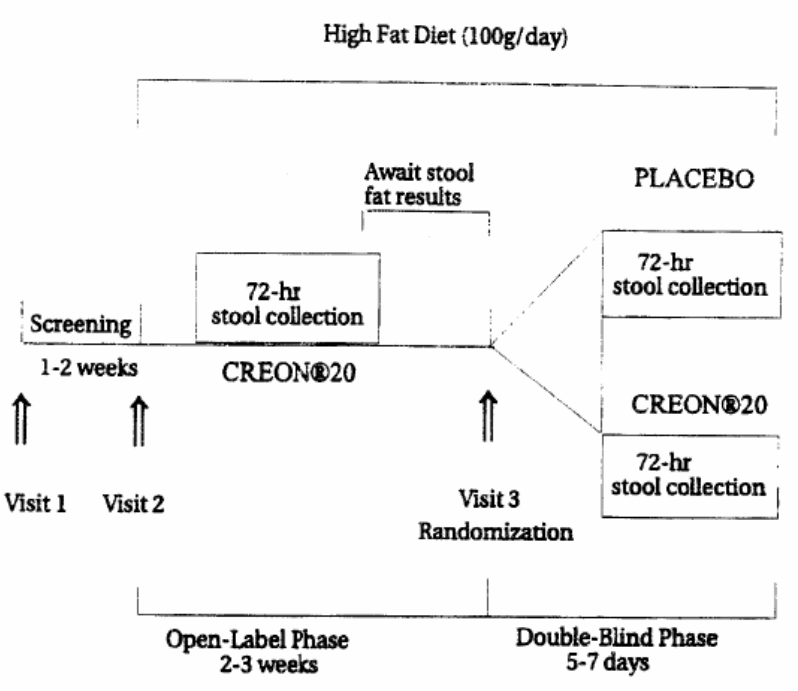
6.1.3.3.1.1 Design, Treatment, Dose, and Population

The Prior Pediatric CF Study was a randomized-withdrawal, double-blind, placebo-controlled, multi-center study in patients with CF, ages 7 to 17 years. The study was four to six weeks in duration, including a one- to two-week screening period, a two- to three-week open-label Creon treatment phase, and five- to seven-day double blind phase wherein patients were treated with either Creon or placebo. Forty-seven patients were enrolled and treated with open-label Creon® 20 (MMS; 20,000 lipase units) with individualized dosing. All patients were treated with a high-fat diet (at least 100 grams of fat/day) from the beginning of the open-label phases through the completion of the study.

The first of two 72-hour stool collections for CFA was begun after at least 48 hours of high-fat diet during the open-label Creon treatment phase. After completion of stool collection for the first CFA, patients continued the same individualized Creon dose and high-fat diet for two to three weeks. Patients with initial CFA above 80% while on a high-fat diet and open-label Creon treatment were then randomized into the double-blind phase of the study (total N=38: 18 patients randomized to Creon MMS, and 19 patients to placebo; treatment groups are named by treatment they were randomized to in the DB phase of the study). The second 72-hour stool collection for CFA was begun after 48 hours of treatment during the double-blind phase.

Treatment effect for individual patients was assessed by comparing change in CFA from the open-label treatment phase to the double-blind treatment phase. Primary efficacy was assessed by comparing the mean change in CFA between the Creon and placebo treatment groups during the open-label (Creon treatment) phase compared to the DB (Creon or placebo treatment) phase. Secondary efficacy parameters included change in stool frequency, stool consistency, and clinical global improvement (CGI) scores from the open-label treatment phase compared with the double-blind phase. A diagram of the overall study design is presented in Figure 2 below (electronically reproduced from prior clinical review by Dr. Gibril, 09-December-2003)

Figure 2: Prior Pediatric Cystic Fibrosis Study (S223.2.101), Study Phases



6.1.3.3.1.2 Objectives and Outcomes Measures

The primary objective of the study was to evaluate the effectiveness of Creon® 20 compared to placebo in the treatment of steatorrhea in CF patients with PEI. Efficacy was evaluated by comparing CFA from the open-label, Creon-treatment phase to CFA from the double-blind treatment (with Creon® 20 or placebo) phase. The secondary objectives were to compare the effect of treatment on frequency of bowel movements, stool consistency, and CGI, and assessments of safety during administration of Creon® 20 capsules. Safety parameters were summarized by treatment group and included any changes in physical examinations and vital signs, and routine clinical laboratory examination (including urine and serum uric acid monitoring), and the occurrence during treatment with Creon of adverse events.

6.1.3.3.1.3 Patient Eligibility/Inclusion and Exclusion Criteria

Patients were eligible for study participation if they were 7 to 17 years old, had a diagnosis of CF (by two sweat chloride tests), had clinical symptoms of PEI, and had a history of steatorrhea. Patients were excluded from study participation if they had a forced expiratory lung volume in one second (FEV1) of less than 25% or clinically severe pulmonary disease, required the ingestion of medium chain triglycerides as nutritional supplements, had abnormal serum uric acid on screening, or had concurrent use of non-study PEPs. Patients could not have received antacids or other acid suppressants, prokinetic drugs, or antibiotics known to have caused diarrhea in the 30 days prior to screening.

6.1.3.3.2 Prior Adult CF Study (S223.2.102)

The design of the Prior Adult CF study is identical to the Prior Pediatric CF study summarized above, except that patients in this study were 18 years and older at time of enrollment. Fifty patients were enrolled and treated with open-label Creon® 20 and a high-fat diet, and 36 patients were proceeded to the randomized double-blind phase of the study (total N=36: 18 patients randomized to Creon MMS, and 18 patients to placebo).

6.1.3.3.3 Prior Adult CP Study (223.2.01)

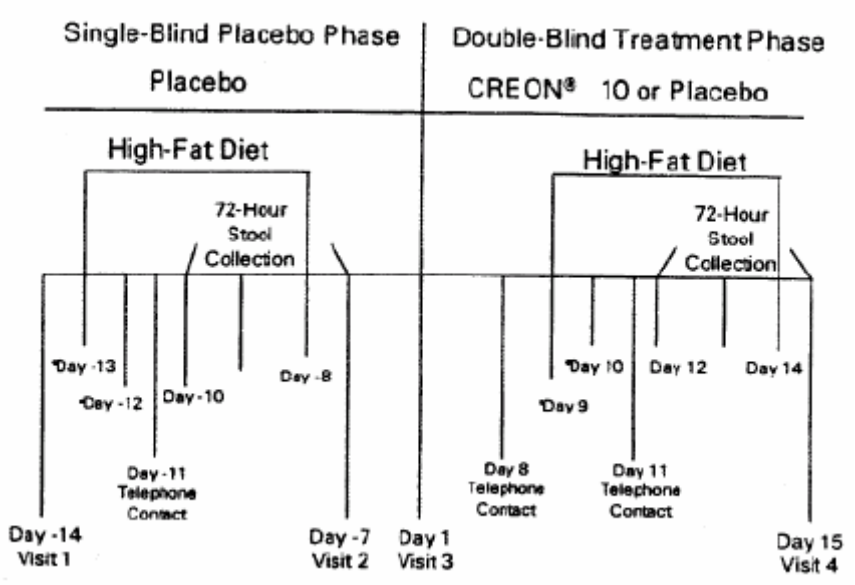
6.1.3.3.3.1 Design, Treatment, Dose, and Population

The Prior Adult CP study was a randomized, double-blind, placebo-controlled, study of Creon® 10 (MMS; 10,000 lipase units) in adult patients with CP, ages 38 to 74 years. The study consisted of two consecutive, two-week, outpatient phases: a single-blind, placebo run-in/wash-out phase, and a randomized, double-blind treatment (Creon or placebo) phase. Patients were to consume a high-fat diet from the beginning of the single-blind placebo phase through completion of the double-blind treatment phase.

Sixty-four patients entered the single-blind, placebo run-in phase. Since many of the patients were receiving treatment with PEPs prior to study entry, this phase served as a PEP wash-out phase. Patients with CFA less than 80% or stool fat greater than 10 gram/day, or both, during the placebo run-in phase proceeded to the double-blind treatment phase, where they were randomized to treatment with either Creon® 10 or placebo (total N=27; 13 patients randomized to Creon MMS, and 14 patients to placebo). The Creon dose during the study was four capsules (40,000 lipase units) per meal and two capsules (20,000 lipase units) per snack, with a minimum of 10 capsules (100,000 lipase units) per day and a maximum of 24 capsules (240,000 lipase units) per day.

Treatment effect for individual patients was assessed by comparing change in CFA from the single-blind placebo phase to the double-blind treatment phase (Creon® 10 or placebo). Primary efficacy was assessed by comparing the mean change in CFA between the Creon treatment and placebo groups during the double-blind phase (Creon or placebo) compared to the single-blind placebo phase. The Primary efficacy endpoint was difference in mean CFA between the placebo and treatment groups during the double-blind treatment phase. The study phases are presented in Figure 3 below (electronically reproduced from prior clinical review by Dr.Gibril, 09-December-2003).

Figure 3: Prior Adult Chronic Pancreatitis Study (223.2.01), Study Phases



6.1.3.3.3.2 Objectives and Outcomes Measures

The objective of the study was to compare the efficacy of Creon®10 versus placebo on change in CFA from the single-blind placebo phase compared to the double-blind treatment phase. Safety was assessed by the evaluation of safety variables including change from Baseline in medical history, physical examinations, and laboratory analyses, and the occurrence of adverse events.

6.1.3.3.3.3 Patient Eligibility/Inclusion and Exclusion Criteria

Patients were eligible for study participation if they had a clinical history consistent with CP, and confirmation of CP diagnosis by one of the following criteria: computed-tomography, endoscopic retrograde cholangiopancreatography (ERCP), or pancreatic calcification on abdominal x-ray or ultrasound. Patients must also have had evidence of active PEI demonstrated by at least one of the following: steatorrhea, secretin test, serum trypsin, or PABA urinary test, and the use of any PEP for the entire six months preceding study entry. Patients were excluded from study participation if they had CF, severe systemic disease, or had been diagnosed with an ileus, acute abdomen, or acute pancreatitis within the two months preceding study entry.

6.1.4 Efficacy Findings

Detailed reviews of the efficacy findings from the New Infant CF Study and New Adult PEI studies were performed, and are summarized in the Appendix in the Individual Study Reports section.

The key efficacy findings from the New Infant CF and the New Adult PEI studies are summarized below. The determination of efficacy is based solely on primary efficacy endpoints and results of secondary efficacy measures are not discussed. The reader is directed to the individual study reports

in the Appendices of this document for discussion of secondary endpoints of the New Infant CF and New Adult PEI studies.

Likewise, the key efficacy findings from the previously reviewed Prior Pediatric CF, Prior Adult CF and Prior Adult CP studies were based solely on primary efficacy endpoints and the results of secondary efficacy measures of those three studies are not discussed.

6.1.4.1 New Infant CF Study (S248.3.003)

The primary efficacy endpoint in the New Infant CF study was change from Baseline (no-treatment) CFA compared to Creon treatment period CFA in the Intent-to-treat (ITT) population.

All twelve infants with PEI due to CF were successfully screened and enrolled, completed the study, and were included in the ITT analysis. There were five males and seven females, ranging in age from one through 23 months. For the primary endpoint, there was a clinically meaningful increase in CFA from Baseline compared to treatment with Creon. The mean Baseline CFA was 58%, the Creon treatment period mean CFA was 85%, and change in mean CFA was 27% (95% C.I. [12.9, 40.4]).

Because treatment effect has been reported to be more clinically apparent in patients with lower Baseline CFA,[1] this Reviewer also performed an unplanned subgroup analysis comparing the mean change in CFA from Baseline in patients with a Baseline CFA <60% (N=4), and in patients with a Baseline CFA ≥60% (N=8). For the subgroup of patients with a Baseline CFA <60%, the mean Baseline CFA was 41%, the mean increase in CFA while on Creon treatment was 43% (95% C.I. [-0.9, 86.1]). Although the results show a large increase in mean CFA in these patients from Baseline compared to Creon treatment, the mean change in CFA is not statistically significant, most likely due to the small number of patients in this subgroup. For the subgroup of patients with a Baseline CFA ≥60%, the mean Baseline CFA was 66%, and the mean change in CFA was 19% (95% C.I. [6.8, 30.6]). These findings are clinically meaningful but not statistically significant due to the small number of patients studied.

This Reviewer concludes the findings are supportive of efficacy. The results of the primary efficacy analysis and for the subgroup analyses (by Baseline CFA <60% or ≥60%) are summarized in the following table (from Dr. Castillo's Review):

Table 2: Study S248.3.003; Change in CFA (%) by Baseline CFA (%) Category for ITT Population

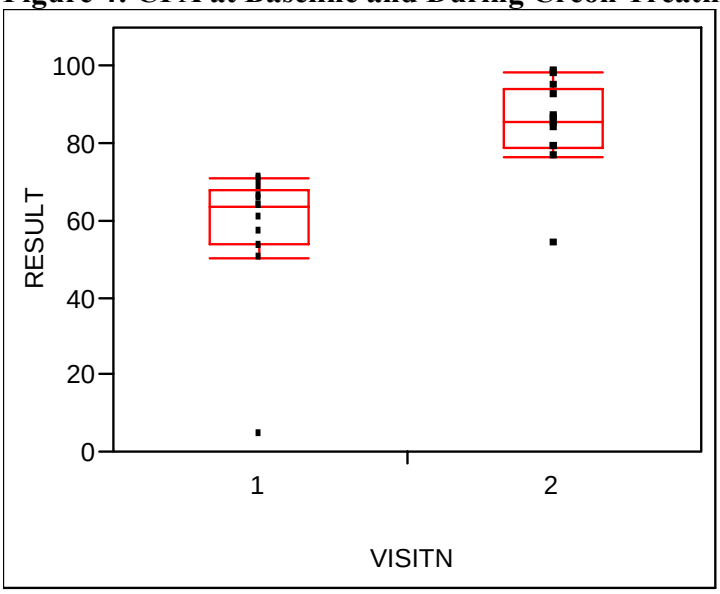
	All Patients	Baseline CFA<60	Baseline CFA≥60
n	12	4	8
Baseline mean (%)	58.0	41.4	66.4
Mean change from baseline (95% C.I.)	26.7 (12.9, 40.4)	42.6 (-0.9, 86.1)	18.7 (6.8, 30.6)

Source: Statistical Reviewer's analysis

The results for CFA at Baseline (no-treatment) and for CFA during Creon treatment for the ITT population are presented graphically in the following figure, Figure 4.

Explanation of Figure 4: The VISITN 1 column represents Baseline encounters and the VISITN 2 column represents encounters during Creon treatment. Each data point along the Y (RESULT) axis represents an individual patient's CFA reported in percent units. The bottom of each closed box delimits the lowest 25th percentile of CFA and the top of each box delimits the upper 75th percentile of CFA. The bottom line under each box delimits the lower 5th percentile of CFA and the topmost line above each box delimits the upper 95th percentile of CFA. The horizontal line within each box represents the median CFA for each treatment period. The dots below the boxes are outliers.

Figure 4: CFA at Baseline and During Creon Treatment in the ITT Population



RESULT: Coefficient of Fat Absorption (CFA)
VISITN: Baseline visit (1), treatment period visit (2).

In summary, a clinically meaningful increase in CFA was demonstrated for the ITT population. Increase in CFA while on treatment compared to no-treatment baseline tended to be greatest in patients with lowest Baseline CFA. These findings provide clinically meaningful evidence that Creon MMS (CMP) augments pancreatic lipase activity. This Reviewer concludes that the results support the efficacy of Creon for infants with CF-related PEI at the dose studied.

6.1.4.2 New Adult PEI Study (S245.3.115)

The primary efficacy endpoint in the New Adult PEI study was change in CFA from non-treatment (single-blind placebo) baseline phase compared to the DB (Creon or placebo treatment) phase for the ITT population.

Of 156 patients who were screened, 95 patients were enrolled and one patient withdrew consent prior to starting the study, leaving 94 patients in the ITT. Of these 94 patients, 30 patients were randomized to treatment in the placebo group, 31 patients in the 1.5 gram/day (low-dose) group, and 33 patients in the 3.0 gram/day (high-dose) group. Baseline demographic data showed that 35 patients had chronic pancreatitis and 59 had pancreatectomy. All patients were Asian, and 81% of patients were male. Seventy-nine patients had a history of PEP exposure prior to study entry. There were no important differences between the treatment groups by Baseline demographic criteria.

Results for the primary efficacy endpoint, change in CFA from non-treatment (single-blind placebo) Baseline phase compared to the DB (Creon or placebo treatment) phase for the ITT population, showed that change in mean CFA from Baseline to DB treatment was 4% for the placebo group, 11% for the low-dose group, and 16% for the high-dose group. Compared to the placebo group, mean CFA change for the low-dose group was 7% (p-value = 0.144), and mean CFA change in the high-dose group was 12% (p-value = 0.015). The clinical meaning of these results is unclear due to an unplanned interim analysis discussed at the end of this section. This Reviewer concludes that these findings can not be used to support efficacy.

This Reviewer also performed subgroup analyses of the primary endpoint for the PY and CP subgroups. For the CP subpopulation, change in mean CFA from Baseline to DB treatment was 5% for the placebo group, 9% for the low-dose group and 7% for the high-dose group. Compared to the placebo group, mean CFA change for the low-dose group was 4% (p-value = 0.540), and mean CFA change in the high-dose group was 2% (p-value = 0.781). The clinical meaning of these results is unclear due to an unplanned interim analysis discussed at the end of this section. This Reviewer concludes that these findings can not be used to support efficacy.

For the PY subpopulation, change in mean CFA from Baseline to DB treatment was 3% for the placebo group, 12% for the low-dose group and 20% for the high-dose group. Compared to the placebo group, mean CFA change for the low-dose group was 9% (p-value = 0.180), and mean CFA change in the high-dose group was 18% (p-value = 0.011). The clinical meaning of these results is unclear due to an unplanned interim analysis discussed at the end of this section. This Teviewer concludes that these findings can not be used to support efficacy.

The preceding findings are summarized in Table 3 below (from Dr. Castillo's review).

Table 3: New Adult PEI Study—Change in Coefficient of Fat Absorption for All Patients by Diagnosis, ITT Population[1]

	Creon 1.5 g/day [3]	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.) [2]	7.1 (4.8)	11.6 (4.7)	
p-value for Mean Treatment Difference	0.144	0.015	
Chronic Pancreatitis			
n	11	11	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	

[1] Source: Statistical Reviewer's Analysis based on ANOVA model with treatment as factor.
[2] Standard Error
[3] One patient included in the FAS in the 1.5 g/day group did not have treatment period CFA performed/recorded thereby reducing n from 31 to 30 patients.

The study results showed a significant increase in CFA compared to the placebo group was demonstrated for the high-dose Creon treatment group for the overall (ITT) study population. A significant increase in mean CFA compared to the placebo group was also demonstrated for the high-dose Creon treatment group for the PY subpopulation; however, the increase in CFA did not reach 30%. No significant change in CFA compared to the placebo group was demonstrated for the low-dose group for the overall study population, or in either the PY or CP sub-populations. No difference in mean change in CFA in either the low- or high-dose groups compared to the placebo group seen in the CP subpopulation.

Of note, there were seven patients in any Creon CMP treatment group with a Baseline CFA less than 40%, including five patients in high dose PY sub-population and two patients in the low dose PY sub-population. No patients in the CP sub-population who received Creon CMP had Baseline CFA less than 40%.

It was additionally noted that the mean Baseline CFA in the placebo-treated patients was lower overall, and especially, in the CP sub-population, as compared to the high-dose Creon treatment group (and to a lesser extent the low-dose Creon treatment group). Specifically, mean Baseline CFA in the high-dose CP sub-population was 78%, which was about 21% higher than the placebo-treated CP sub-

population, and 16% higher than the high-dose PY sub-population. These findings indicate that based on mean CFA levels at Baseline: 1) the potential for the high-dose Creon CP sub-population to respond to treatment was lower than in the placebo-treated CP sub-population, which may account for the lack of response seen in that group; and 2) the potential to respond was higher in the high-dose PY sub-population, which may explain the trend toward increase in CFA with treatment in this sub-population. Thus, this Baseline mean CFA imbalance may have affected the overall results for the study, as the high-dose Creon treatment had a lower capacity to respond, resulting in a lower likelihood of detecting a treatment difference between the groups.

In summary, a significant increase in mean CFA in the high-dose Creon group compared to placebo was demonstrated in the overall ITT population. No significant difference in mean CFA compared to placebo was demonstrated in the low-dose Creon group (overall or by subpopulation), or in the CP subpopulation with either Creon dose.

Amendments critical to the efficacy review are now described:

Two related protocol amendments critical to the review are now described. One amendment increased the size of each treatment group from 18 to 25 patients. The Sponsor states that the protocol was amended because a prior amendment allowed for a blinded, un-planned interim analysis to be performed. The blinded analysis was performed on the subset of patients who had at that time completed both the single-blind non-treatment phase and the double-blind (treatment or placebo) phase.

The Sponsor reports that the interim analysis suggested that the original study was underpowered to detect the expected change in CFA between the Creon-treated groups compared to the placebo group. Therefore, group size was increased from 18 to 25 patients per treatment arm to ensure a 90% power at a two-sided significance level of 5%. The Statistical Reviewer, Dr. Sonia Castillo, concludes that since the interim analysis was not pre-specified and the potential effects on measures of statistical success were not provided, no statistical inferences of the efficacy results can be made.

A trend towards increased CFA (primary efficacy point) with high-dose treatment in the overall population and the high-dose PY subgroup is suggested. However, this Reviewer concludes that the efficacy findings of the New Adult PEI cannot be used to support efficacy of Creon CMP for the treatment of PEI due to PY or CP due to the statistical issues outlined in the preceding paragraph. Further, efficacy was not demonstrated in the low-dose treatment arms, or in the CP group at any dose.

6.1.4.3 Efficacy results of previously reviewed pivotal trials.

6.1.4.3.1 Prior Pediatric CF Study (S223.3.101)

The Prior Pediatric CF study was a double-blind, placebo-controlled, randomized-withdrawal study of Creon CMP in pediatric patients with CF, ages seven to 17 years. The primary efficacy endpoint was change in CFA from Baseline (OL Creon treatment) compared to CFA on DB treatment (Creon or placebo). Patients must have had a Baseline CFA of <80% to enter to DB phase of the study. Forty-

seven patients entered the study and completed the OL Creon treatment phase, and 38 patients qualified for randomization to the DB treatment phase of the study. The ITT population included 37 patients: One patient withdrew prior to randomization, 18 patients were randomized to Creon (Creon group) and 19 were randomized to placebo (placebo group). The mean Creon® 20 dose taken during the double-blind phase was 7,855 lipase units/kg/day. Gender distribution across the two treatment groups was approximately even. Patient ages ranged from 7 to 17.9 years, and racial representation was 95% Caucasian, 2% Black, and 2% Other.

The results show that both treatment groups had a similar mean Baseline CFA. The placebo group had a mean CFA of 86% and the Creon group had a mean CFA of 87%. After randomized-withdrawal during the DB treatment phase, the placebo group had a mean CFA of 52%, which is a decrease in mean CFA of 34. In the DB treatment phase, the Creon group had a mean CFA of 84%, which was essentially unchanged from Baseline (change in mean CFA in the Creon group of -3). The overall results for the primary efficacy endpoint show a statistically significant and clinically meaningful mean difference between the two groups in favor of Creon treatment, with CFA 35% higher in the treatment arm (p-value <0.001). The results are summarized Table 4 below (electronically reproduced from previous clinical review, by Dr. Gibril, September 2003).

Table 4: Prior Pediatric CF Study, Primary Endpoint Result (Change in Mean CFA

	Mean CFA (%)						
Protocol	**Open-label (OL) (Run-in phase) treatment**		**Double-blind (DB) treatment**		**Change from OL to DB**		**p-value***
	Placebo N= 19	Creon N= 18	Placebo N=19	Creon N=18	Placebo N=19	Creon N=18	
S2233101	86%	87%	52%	84%	-34%	-3%	<0.001
*p-value for comparison of the two treatment groups for change in CFA from OL to DB treatment							

This Reviewer agrees with conclusions of the prior clinical review team that the results demonstrate a statistically significant and clinically meaningful benefit for the use of Creon CMP in children 7 through 17 years old with PEI due to CF.

6.1.4.3.2 Prior Adult CF Study (S223.3.102)

The Prior Adult CF study was a double-blind, placebo-controlled, randomized-withdrawal study of Creon CMP in adult patients with CF. The primary efficacy endpoint was change in CFA from Baseline (OL Creon treatment) compared to CFA on DB treatment (Creon or placebo). Patients must have had a Baseline CFA of <80% to enter to DB phase of the study. Fifty patients entered the study and completed the OL Creon treatment phase, and 36 patients qualified for randomization to the DB treatment phase of the study. The ITT population was comprised of all 36 qualifying patients: 18 patients were randomized to Creon (Creon group) and 18 were randomized to placebo (placebo group). The mean Creon® 20 dose taken during double-blind phase was 4,537 lipase units/kg/day. Baseline gender composition was 40% female and 60% male, which was approximately evenly distributed across the treatment groups. Patient ages ranged from 18 to 53 years, and racial representation was 100% Caucasian.

The results show that both treatment groups had a similar mean Baseline CFA. The placebo group had a mean CFA of 88% and the Creon group had a mean CFA of 89%. After randomized-withdrawal during the DB treatment phase, the placebo group had a mean CFA of 51%, which is a decrease in mean CFA of 35. In the DB treatment phase, the Creon group had a mean CFA of 87, which was essentially unchanged from Baseline (change in mean CFA in the Creon group of -2). The overall results for the primary efficacy endpoint show a statistically significant and clinically meaningful mean difference between the two groups in favor of Creon treatment, with CFA 32% higher in the treatment arm (p-value <0.001). The results are summarized in Table 5 below (electronically reproduced from previous clinical review, by Dr. Gibril, September 2003).

Table 5: Prior Adult CF Study, Primary Endpoint Result (Change in Mean CFA)

	Mean CFA (%)						
Protocol	**Open-label (OL) (Run-in phase) treatment**		**Double-blind (DB) treatment**		**Change from OL to DB**		**p-value***
	Placebo N=18	Creon N=18	Placebo N=18	Creon N=18	Placebo N=18	Creon N=18	
S2233102	88%	89%	51%	87%	-37%	-2%	<0.001
*p-value for comparison of the two treatment groups for change in CFA from OL to DB treatment							

This Reviewer agrees with conclusions of the prior clinical review team that the results demonstrate a statistically significant and clinically meaningful benefit for the use of Creon CMP in adults, 18 years and older, with PEI due to CF.

6.1.4.3.3 Prior Adult CP Study (223.2.01)

The Prior Adult CP study was a randomized, double-blind, placebo-controlled study of Creon CMP in adult patients with CP. The primary efficacy measure was change in CFA from the single-blind (SB) placebo phase compared to CFA during DB phase (placebo or Creon treatment). The study endpoint was the comparison of the difference in mean change in CFA between the placebo and treatment groups. Patients must have had a Baseline (single-blind placebo treatment) CFA of <80% or stool fat ≥10 g/day to enter to DB phase of the study. Sixty-four patients entered the single-blind (placebo) treatment phase of the study, and 27 patients underwent randomization to the DB treatment phase of the study: 13 patients were randomized to Creon treatment (Creon group) and 14 patients were randomized to placebo treatment (placebo group). One patient in the Creon group was excluded from the efficacy analysis due to missing data (lost stool collection), which reduced the ITT population to 26 patients. The mean Creon® 10 dose taken by the treatment group was 1,780 units/kg/day. Patient ages ranged from 31 to 74 years. There were nine females and 18 males, and there were 17 Caucasian and ten Black patients. There were no imbalances between the treatment groups by Baseline demographic data.

The results show that both treatment groups had a similar mean Baseline CFA. The placebo group had a mean Baseline CFA of 56% and the Creon group had a mean Baseline CFA of 50%. In the

randomized DB treatment phase, the placebo group had a mean CFA of 68%, which was an increase in mean CFA of +12%. In the DB treatment phase, the Creon group had a mean CFA of 87, which was an increase in mean CFA of +37%. Comparison between the two treatment groups showed that the Creon group had a larger mean increase in CFA compared to the placebo group that was clinically meaningful and statistically significant (p=0.0185). These results are summarized in Table 6 below (electronically reproduced from previous clinical review, by Dr. Gibril, September 2003).

Table 6: Prior Adult CP Study (), Primary Endpoint Results (Change in Mean CFA

	Mean CFA (%)						
Protocol	**Single-blind (SB) placebo phase**		**DB treatment phase**		**Change from SB to DB**		
	Placebo N=14	Creon N=12	Placebo N=14	Creon N= 12	Placebo N=14	Creon N= 12	**p-value***
223.2.01	56%	50%	68%	87%	12%	37%	0.0185
*p-value for comparison of the two treatment groups for mean change in CFA from SB to DB treatment							

This Reviewer concurs with the previous clinical review team's conclusions that the Prior Adult CP study provides statistically significant and clinically meaningful evidence of clinical efficacy for Creon compared to placebo for mean change in CFA from single-blind (placebo) to DB treatment.

6.1.5 Efficacy Conclusions

The efficacy of Creon TbMP has not been demonstrated.

The Sponsor intends to market Creon TbMP, for which no efficacy and safety clinical trials have been conducted. The Sponsor states that data from the five clinical short-term efficacy and safety studies demonstrate that Creon CMP is effective in the treatment of steatorrhea due to PEI in patients with CF, CP, and PY. The three previously reviewed studies support efficacy. The New Infant CF Study provides supportive evidence of efficacy; however, the findings do not reach clinical significance due to the small study size. The New Adult PEI study does not provide convincing evidence of efficacy. Lastly, the Bridging study, conducted for the purpose of demonstrating the comparability of the Creon CMP and TbMP products, failed to demonstrate the clinical comparability of the two products. Therefore, the efficacy of Creon TbMP has not been demonstrated.

In this CR amendment, two new short-term efficacy and safety studies were submitted that were amenable to substantive review. These two studies, the New Infant CF study and the New Adult PEI, showed the following results:

- The New Infant CF study evaluated change in CFA from Baseline (non-treatment) phase to Creon treatment phase in 12 infants, ages one to 24 months, with PEI due to CF. Mean increase in CFA was 27% (95% C.I. 12.3, 41.1), and the increase in CFA with treatment was greatest in four patients with Baseline CFA below 40%. The Statistical Reviewer concluded that the small study size precluded statistical inferences. Nevertheless, these findings are

consistent with results seen in children and adults in the Prior Pediatric CF and Prior Adult CF studies.

This Reviewer concludes that while statistical inferences can not be drawn, the results are clinically meaningful. In conclusion, this study supports the short-term efficacy of Creon treatment in infants with CF, and use down to one month of age is supported and may be reflected in labeling.

- The New Adult PEI study evaluated change in CFA from non-treatment (SB placebo) phase to DB treatment (Creon or placebo) phase in adults with PEI due to CP or PY. Compared to the placebo group, the mean CFA change for the low-dose group was 7% (p-value = 0.144), and mean CFA change for the high-dose group was 12% (p-value = 0.015). In the PY sub-population, mean increase in CFA for the high-dose group compared to placebo was 18% (p-value = 0.011), and in the CP sub-population was 2% (p-value = 0.781).

  Overall, the study results show a significant increase in mean CFA in the high-dose Creon group compared to placebo in the ITT population and in the PY sub-population. No significant difference in mean CFA compared to placebo was demonstrated in the low-dose Creon group (overall or by sub-population), or in CP patients treated with either low-dose or high-dose Creon CMP.

  Imbalances between the treatment groups by Baseline mean CFA may have affected the overall results of the study. The placebo group had the lowest Baseline CFA and the high-dose Creon treatment group had the highest CFA. This imbalance may have affected the overall study results since there was a lower likelihood of detecting a difference between the placebo and high-dose Creon groups as the high-dose group had a lower capacity to respond to active treatment.

  The Sponsor performed a non-pre-specified interim analysis, which suggested that the original study was underpowered to detect the expected change in CFA between the Creon-treated groups compared to the placebo group. Therefore, group size was increased from 18 to 25 patients per treatment arm. The Statistical Reviewer, Dr. Sonia Castillo, concludes that since the interim analysis was not pre-specified and the potential effects on measures of statistical success were not provided, no statistical inferences of the efficacy results can be made.

  Thus, it is the assessment of this Reviewer that the clinical findings of the New Adult PEI do not support the efficacy of Creon CMP for treatment adult patients with PEI due to PY or CP.

Three clinical short-term efficacy and safety studies were previously reviewed during the original NDA review cycle for Creon. These studies were assessed by the Clinical Review Team as having demonstrated statistically significant and clinically meaningful evidence of clinical efficacy for Creon (by change in CFA) in pediatric (ages 7 years and older) and adult patients with CF, and in adult patients with CP. These three studies showed the following results:

- In the Prior Pediatric CF Study (S2233101) after randomized-withdrawal from Baseline Creon treatment to DB treatment with placebo or Creon, mean CFA in the Creon treatment group was 31% higher than mean CFA in the placebo group (p-value < 0.001). These results showed a statistically significant and clinically meaningful benefit in favor of Creon treatment for difference in mean CFA between the Creon and placebo groups in pediatric patients with CF.

- In the Prior Adult CF Study (S2232102) after randomized-withdrawal from Baseline Creon treatment to DB treatment with placebo or Creon, mean CFA in the Creon treatment group was 35% higher than mean CFA in the placebo group (p-value < 0.001). These results showed a statistically significant and clinically meaningful benefit in favor of Creon treatment for difference in mean CFA between the Creon and placebo groups in adult patients with CF

- In the Prior Adult CP Study (223201), mean change in CFA from Baseline (SB placebo treatment) to DB treatment (Creon or placebo) was 25% higher in the Creon treatment group than in the placebo group (p-value <0.0185). These results showed a statistically significant and clinically meaningful benefit in favor of Creon treatment for difference in mean CFA between the Creon and placebo groups in adult patients with CP.

In conclusion, it is the overall assessment of this Reviewer that data from three short-term clinical efficacy and safety studies conducted in pediatric and adult patients with CF, and adult patients with CP support the effectiveness of Creon CMP treatment of steatorrhea in patients with EPI, and that Creon's effectiveness appears to be greatest in the most severely affected patients (i.e., patients with the lowest Baseline CFA). Results from the New Infant CF study were supportive of the clinical effectiveness of Creon CMP in the treatment of steatorrhea in infants with CF, ages one to 24 months these patients, and the results from this study were consistent with the results seen in clinical studies in older pediatric and adult patients. These findings support the labeling of Creon CMP for the treatment of steatorrhea in patients with EPI, ages one month to adult. The results from the New Adult PEI study cannot be used to support the effectiveness of Creon CMP in the treatment of EPI, due to problems with study conduct, and because of the results of the study were not clinically meaningful.

The Sponsor intends to market the Creon TbMP. However, no efficacy and safety clinical trials have been conducted to date with the Creon TbMP. The Bridging study that was submitted to the CR amendment, and was conducted for the purpose of demonstrating the comparability of the Creon CMP and TbMP products, failed to demonstrate the clinical comparability of the two products. Thus, the efficacy and safety results from studies with the Creon CMP cannot be used to support the clinical efficacy and safety of the Creon TbMP. Therefore, the efficacy (and safety) of the Creon TbMP for the treatment of steatorrhea in patients with EPI has not been demonstrated, and the information submitted in this CR amendment does not support the approval of Creon TbMP.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This Complete Response (CR) amendment includes safety information from the NDA Safety Update (Integrated Safety Summary; ISS). This ISS contains information from 57 clinical studies conducted between July 1985 and May 2006, and performed with Creon MMS (CMP) or other formulations that are no longer marketed (e.g., Creon MS). All patients who received at least one partial dose of Creon MMS and Creon MS were included in the safety population. Safety reporting is through 30-June-2006, and there were no ongoing studies at the time of submission.

The safety of the TbMP has not been evaluated in clinical trials, with the exception of single-dose Creon TbMP administration to nine patients in the Bridging study. Since the clinical comparability of the Creon CMP to the TbMP was not demonstrated in the Bridging study, safety data obtained with the CMP can not be solely relied upon to establish the safety of the TbMP.

Of the 57 studies in the ISS, 52 are multiple-dose studies and five are single-dose studies. Safety information from 12 of the 57 studies is submitted for the first time in this CR amendment. Seven studies were not incorporated into the ISS due to data quality issues (e.g., inadequate methods for data collection, and incomplete safety datasets), and were not included in this safety review. Therefore, the ISS contains safety information from 50 studies.

Sufficient safety information was provided in the CR amendment to allow substantive review of the two newly submitted studies for safety: the New Infant CF Study and the New Adult PEI Study. These studies have been individually reviewed for safety by this Reviewer.

Because children with CF are an important treatment population for the PEPs, this Reviewer also assessed the safety of Creon MMS in children with CF. Insufficient safety information was provided in the CR amendment to allow substantive review of all studies of Creon MMS (CMP) in children; however, there was sufficient information available to permit a safety review of three pediatric CF safety studies (e.g., electronic safety datasets) in addition to the Infant CF Study. Thus, this Reviewer performed a pooled safety analysis of four CF pediatric studies, including the New Infant CF Study, and three additional open-label safety studies of Creon CMP in pediatric CF patients: the Prior Infant CF Safety, Prior Pediatric CF Safety Study, and Prior Young Adult CF Safety Study. These three additional studies included pediatric CF patients from six months through 18 years of age, and included approximately 150 patients. The designs of these three additional studies are described as follows:

The Prior Infant CF Safety Study (S245.3118) was an open-label, randomized, cross-over study of Creon MMS and a Creon formulation designated “Creon for Children” (CFC; a non-US marketed formulation of MMS) in infants with PEI due to CF, six to 36 months old. The primary outcome measure was parental preference of either formulation. Forty (40) patients were randomized and underwent a non-treatment period of one to two weeks. Nineteen patients received CFC for two weeks followed by Creon MMS for two weeks (CFC>MMS), and 21 patients received Creon MMS

for two weeks followed by CFC for two weeks (MMS>CFC). One patient randomized to CFC>MMS withdrew during the first treatment period due to nausea, vomiting, and diarrhea. Mean exposure to CFC and Creon MMS was 14 days each.

The Prior Pediatric CF Safety Study (S245.3105) was an open-label, randomized, cross-over study of Creon 10,000 (Creon MMS) or Creon 8,000 (Creon MS) in children with PEI due to CF, three to 17 years old (the individual study report is not available for review and this summary is taken from pages 8,479 and 8,480 of volume 24 of the sponsor's CR amendment; further details were not available). The primary efficacy outcome measure was comparison of CFA between the two treatment groups. There was no placebo treatment group and there was no open-label non-treatment period. Following a two-week run-in period with Creon 8,000 MS, patients received either four weeks of Creon MMS followed by four weeks of Creon MS, or four weeks of Creon MS followed by four weeks of Creon MMS. Fifty-nine (59) patients were entered in the study, including 11 patients less than 7 years old, 28 patients ages 7 to less than 12 years old, and 20 patients ages 12 to less than 18 years old. Only 57 of these 59 patients received Creon MMS.

The Prior Young Adult CF Safety Study (K245.5004) was a randomized, double-blind, cross-over study in patients four years and older with CF (N=34) that compared the CFA during treatment with Creon MMS to Creon MS. There was no placebo treatment group and there was no open-label non-treatment period. The study design included a two- to three-week run-in period with Creon 8,000 MS followed by two crossover periods of two weeks each, in which Creon 10,000 MMS and Creon 8,000 MS were given in random order. Thirty-four (34) patients were entered in the study, including 14 patients ages 7 to less than 10 years old, 14 patients ages 10 to less than 18 years old, and six patients ages 18 to 31 years. Exposure to Creon MMS was for two weeks.

These three studies were reviewed and summarized for safety only. Substantive review for efficacy of these three trials was not possible due to lack of uniform drug treatments, dosage regimens, and controls.

Table 7 below lists the individual studies that were reviewed and summarized for safety in this CR amendment review.

Table 7: Safety Items Reviewed

Item Reviewed	Full or Summary Review	Comment
Integrated Summary of Safety (ISS)	Full	
New Infant CF Study (S248.3.003)	Full	Open label (OL), single-arm study in 12 infants, age 1-24 months. 7-10 day placebo (P) Baseline (BL) phase, followed by OL treatment with Creon MMS for 8 weeks. Safety measures were collected from start of placebo period through end of 8 weeks of treatment.
New Adult PEI Study (S245.3115)	Full	2-3 weeks, randomized (R), double blind (DB), PC trial of two doses of Creon MMS in 94 adult patients with pancreatectomy (PY) or chronic pancreatitis (CP). Safety measures were collected from start of placebo period through end of 2-3 weeks of DB (Creon or placebo) treatment.
Prior Infant CF Safety Study (S245.3118)	Summary	R, OL, cross-over (CO) study of CFC and Creon MMS in 36 infants 6-36 months old. 2 weeks of CFC followed by 2 weeks of MMS, or 2 weeks of MMS followed by 2 weeks of CFC.
Prior Pediatric CF Safety Study (S245.3105)	Summary	10 week, R, OL, CO study of Creon MMS and MS in children, 3-17 years. 2 week P run-in followed by either 4 weeks of MS followed by 4 weeks of MMS, or 4 weeks of MMS followed by 4 weeks of MS.
Prior Young Adult CF Safety Study (K245.5004)	Summary	6 week. R, OL, CO study of Creon MMS and MS in 34 children, 7-31 years. 2 wk P run-in followed by either 2 weeks of MS followed 2 weeks of MMS, or 2 weeks of MMS followed by 2 weeks of MS.

This ISS review was conducted using safety datasets submitted to the CR amendment, including individual safety datasets for the New Infant CF Study and the New Adult PEI Study, and the pooled safety dataset (ADV), which contained all AEs reported in the 50 studies submitted to the ISS. For the purpose of this review, adverse events (AEs) are designated as associated with exposure to drug or placebo within fourteen days, inclusive, prior to the first report of an event. AEs occurring 15 days or more from last exposure are labeled "post-treatment".

7.1.1 Deaths

Eighteen deaths were reported in the Safety Update. Eight deaths occurred in patients who were enrolled in clinical trials described in the ISS. Reports of the remaining ten deaths, which were not described in the ISS, were received from one of two sources: either from one of the seven studies which were not integrated into the ISS, or from non-US post-marketing reports, including compassionate use programs.

Table 8 below displays the eight deaths reported in the ISS by drug treatment group (Creon MMS, Creon MS, Other PEPS, and placebo). Deaths occurred in about 0.3% of patients receiving Creon (MMS or MS) during or within 14 days of treatment, and in about 0.3% of patients receiving placebo during or within 14 days of treatment. No deaths were reported in the ISS in 311 patients during administration of Other PEPs (not shown). This Reviewer concludes that the use of Creon MMS (CMP) is not associated with an increased risk of death as compared to placebo treatment.

Table 8: All deaths in studies reported in the ISS

Deaths, Adverse Events, and Serious Adverse Events included in the ISS	Total		Creon MMS		Creon MS		Any Creon		Placebo	
	n	%[1]	n	%	n	%	n	%	n	%
Patients in NDA Safety Update 2006	1546	100	594	100	991	100	1333	100	589	100
Number of Deaths[2]	8	0.5	1	0.2	3	0.3	4	0.3	2	0.3

[1] Percentage of patients in each treatment group who died
[2] Does not include 10 deaths from post-marketing reports

Of the eight deaths reported in the ISS, five occurred during or shortly after Creon treatment, three occurred during or shortly after placebo treatment, and no deaths were reported during administration of Other PEPs. Of ten deaths reported outside the ISS, all deaths occurred during treatment with Creon, and no deaths were reported during treatment with placebo or Other PEPs.

In the 14 of 18 cases where cause of death could be determined, death appeared to be directly or indirectly attributable to underlying disease. In the three placebo-treated patients who died, one patient's cause of death was not reported, one died of cardiopulmonary decompensation, and one died of cardiovascular failure. In the 15 Creon-treated patients who died, two patients' cause of death was not reported, five patients died of cancer (i.e., metastasis of pre-existing carcinoma), four patients died of cardiopulmonary complications (e.g., due to infection, respiratory failure, and/or complications of CF), two patients died of cardiovascular failure, and one patient each died of ruptured aortic aneurysm, liver failure (due to pancreatic carcinoma), and subdural hematoma. These findings are summarized in Table 9 below. Narrative descriptions of all eighteen deaths are located in Appendix section 10.1.3 of this review.

Table 9: All Deaths Reported In The Complete Response

Study/Patient/ Treatment	Study Description	Cause of Death	Other Clinical Findings	Reviewer's Conclusion
Deaths Reported in Studies Included in the ISS				
223.8.01 Patient 111 11 year old boy; Creon	5-week, OL, CO study of 2 Creon MS preparations in CF	Cardiopulmonary arrest	History of pulmonary complications, methicillin resistant staphylococcus aureus, and depression. Recent fever, chest pain, productive cough and shortness of breath.	Death attributable to complications of underlying disease. Relation to drug unlikely
Creo.630 Patient 7 71 year old man; Creon	R, DB, PC, Creon MS vs. Placebo, Malnutrition in Elderly, No PEI.	Not stated	Parkinsonism and recent onset of urinary tract infection, dehydration, and altered sensorium.	Cause of death not determined from information provided. Relation to drug unknown.
Patient 10 89 year old woman; Creon	See above	Acute cardiac decompensation	History of cardiac insufficiency and atrial fibrillation.	Death due to complications of underlying disease. Relation to drug unlikely
Patient 30 89 year old woman; Creon	See above	Ruptured aortic aneurysm	History of phlebitis and perforated ulcer. Rupture of a previously undiagnosed aortic aneurysm	Death due to complications of an underlying disorder. Relation to drug unlikely
Patient 5 89 year old woman; Placebo	See above	Cardio-pulmonary decompensation	History of angina and asthma Hospitalized with bronchial infection.	Death due to complications of an underlying disorder. Relation to placebo unlikely
Patient 11 87 year old woman; Placebo	See above	Not stated	History of hypertension and "arteriopathy". History of broncho-pulmonary infection, melena, acute anemia, dehydration, and coma.	Cause of death not determined from information provided. Relation to placebo unlikely
Creo.631 Patient 39 77 year old man; Placebo	R, DB, PC, Creon MS vs Placebo. Malnutrition in Elderly, No PEI.	Cardiovascular failure	Carotid and coronary vascular disease, who developed cardiovascular failure.	Death due to complications of an underlying disorder. Relation to placebo unlikely
S245.3.117 Patient 1-C-1 21 year old man; Creon	OL, non-fixed dose of Creon MMS in CF	Not stated	History of pulmonary symptoms related to cystic fibrosis. Cough, respiratory failure, and renal failure developed while on treatment Death due to circulatory failure.	Death due to underling disease. Relation to drug unlikely

Table 9: All Deaths Reported In The Complete Response

Study/Patient/ Treatment	Study Description	Cause of Death	Other Clinical Findings	Reviewer's Conclusion
Deaths In Studies Not Integrated into the ISS or from Non-US Post-Marketing Report				
245.3.103 Patient 2102-L-01 66 year old woman; Creon MMS	Compassionate use program	Metastatic primary carcinoma	History of pancreatectomy due to pre-existing carcinoma of the gall bladder	Death due to underling disease. Relation to drug unlikely
Patient 2170-L-01 55 year old man; Creon	Compassionate use program	Metastatic primary carcinoma	History of pancreatectomy due to pre-existing pancreatic carcinoma	Death due to underling disease. Relation to drug unlikely
Study S245.4.007 Patient 208 85 year old woman; Creon	Protocol not provided	Recurrent primary carcinoma	History of hypertension, Parkinson's, gastric cancer, and pneumonia	Death due to underling disease. Relation to drug unlikely
Patient 403 75 year old woman; Creon	Protocol not provided	Recurrent primary carcinoma	History of pre-existing peritoneal carcinosis	Death due to underling disease. Relation to drug unlikely
Protocol Laugier Patient 22 Age and gender not reported; Creon MS	Protocol not available	Not provided	History of chronic pancreatitis, cardiomyopathy, and positive HIV serology	Cause of death not provided. Relation to drug unknown
Patient 21 38 year old, gender not reported; Creon MS	Protocol not available	Pancreatic Cancer	History of chronic pancreatitis and hypertrophy of the pancreatic head	Death due to underlying disease. Relation to drug unlikely
Study 245.3.104 Patient 2032-O-04 52 year old man: Creon MMS	Protocol not stated	Liver failure due to pre-existing carcinoma	History of pancreatic carcinoma	Death due to underlying disease. Relation to drug unlikely
Patient 1030-C-01 9 year old boy; Creon	Compassionate use not associated with study	Respiratory failure	CF with antecedent pulmonary disease	Death due to underlying disease. Relation to drug unlikely
Patient 2200-C-01 10 year old girl; Creon		Respiratory failure	CF with antecedent pulmonary disease	Death due to underlying disease. Relation to drug unlikely
Patient 2140-L-02 70 year old man; Creon		Subdural hematoma secondary to fall	History of chronic pancreatitis	Death due to trauma. Relation of death to drug unlikely, and relation of fall to drug unknown.

In summary, all of the deaths reported in the ISS appear to be attributable to underlying disease or documented co-morbidities, and there is no indication from these results that treatment with Creon MMS (CMP) is associated with an increased risk of death. No deaths were reported in children less than 18 years old.

7.1.2 Other Serious Adverse Events

This section begins with a brief discussion of the methodological issues related to the safety assessment of patients treated with Other PEPs, followed by reviews of SAEs from the New Infant CF Study, the New Adult PEI Study, and a description of SAEs from the entire ISS. Because of the lack of safety information in children seven years and younger noted in the review of the original NDA, this Reviewer also assessed the types and frequencies of SAEs in the three studies included in the ISS that enrolled infants, children, and young adults with CF (i.e., Prior Infant Safety Study, the Prior Pediatric Safety Study, and Prior Young Adult CF Study).

A direct comparison of safety between Creon MMS and Other PEPs cannot be made for the following reasons: 1) For the 311 patients treated with Other PEPs, only 21 patients participated in the only study reported in the ISS with Creon MMS, Other PEPs, and placebo treatment arms; 2) The ten remaining studies with Other PEP treatment arms (N=290 patients exposed to Other PEPs) did not have a Creon MMS or placebo treatment arm, or a non-treatment Baseline phase; 3) Half of the 311 patients treated with Other PEPs participated in studies where assessment of seriousness and severity of AEs were not done. Therefore, no conclusions can be drawn for comparisons of safety (SAE or non-serious AE) between Creon MMS and Other PEPs, and between Other PEPS and placebo.

7.1.2.1 Serious Adverse Events Reported in the New Infant CF and New Adult PEI Studies

The New Infant CF study included a one-week, open-label, placebo run-in period, and an eight-week, open-label, Creon MMS treatment period in 12 infants with cystic fibrosis, ages one to 24 months. Safety data were collected from the beginning of the placebo period through the eighth week of Creon treatment. No treatment period SAEs were reported, and no deaths were reported.

The New Adult PEI study was a two- to three-week trial of Creon MMS in 94 adult patients with PEI due to chronic pancreatitis (CP) and pancreatectomy (PY). The study began with a one-week single-blind placebo run-in period, followed by a one-week, double-blind Creon MMS treatment period. On completion of the placebo run-in period, patients received seven days of treatment with either placebo, low-dose (1.5 gram/day) Creon (60,000 lipase U/day), or high-dose (3.0 gram/day; 120,000 lipase U/day) Creon. Safety data were collected from the beginning of the placebo run-in phase through the end of the double-blind treatment period.

Three patients experienced SAEs during the single-blind placebo run-in phase, which included hypoglycemia (2 patients), and edema (1). SAEs during the single-blind phase were more common in the placebo group (10%) compared to the low-dose (0%) and high-dose Creon groups (3%). Four patients experienced SAEs during the DB treatment phase. Three patients in the placebo group experienced one SAE each, including pyrexia, subdural hematoma, and hypoglycemia. One patient in the high-dose Creon group experienced pyrexia. No SAE was assessed as being related to study drug, and no SAE resulted in a patient discontinuing from the study. These findings are summarized in Table 10 below which displays incidence rates of AEs, SAEs, and deaths by treatment group.

Table 10: New Adult PEI Study; Summary Incidence of AEs and Deaths during Double-Blind Treatment

Event	Placebo (N=30)			Low-Dose (N=31)			High-Dose (N=33)		
	Events	N	%	Events	N	%	Events	N	%
Any AE	54	19	63	41	23	74	63	23	70
SAE	3	3	10	0	0	0	1	1	3
Deaths	0	0	0	0	0	0	0	0	0

N= number of patients in each study arm.

Thus, in the New Adult PEI Study, treatment with Creon did not appear to be associated with an increased incidence of SAEs in adult patients with PEI as compared to placebo, or by comparison of the high-dose group to the low-dose group, although it is noted that the number of patients treated in this short-term study was small. Although the New Infant Study lacked a control, there were no SAEs reported during this short-term study, and no indication of an SAE safety signal with Creon treatment in these patients.

7.1.2.2 Serious Adverse Events Reported in the ISS

In general on review of the ISS, the types and frequencies of SAEs reported in the Creon-treated patients are similar to SAEs reported in placebo-treated patients, and are similar to those SAEs previously reported in other reviews of Creon and in the existing experience with this product. These findings are generally similar to, and not readily distinguishable from, AEs due to underlying primary disease or are commonly reported complications of primary disease (such as infectious and respiratory complications of CF).

Overall, for all SAEs reported in the ISS, SAEs were reported in 3% of patients receiving Creon MMS, 5% of patients receiving Creon MS, 3% of patients receiving placebo, and 1% of patients receiving Other PEPs. The most commonly reported SAEs by System Organ Class (SOC) across all treatment groups (Creon MMS, Creon MS, Other PEPs, and placebo) were gastrointestinal disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders. The rates of the most commonly reported SAEs by Preferred Term (PT) in the Creon MMS group were pyrexia (0.7%) cough (0.5%), and acute bronchitis (0.3%). The most common SAEs in the placebo group were superinfection of the lung and hypoglycemia (each in 0.5%). Differences noted between the Creon MMS and placebo-treated groups were minor and likely related to underlying diagnoses (e.g. diabetes mellitus). Table 11 below displays SAEs reported in the ISS which occurred in one or more patients treated with Creon MMS, Creon MS, Other PEPs, or Placebo.

Table 11: SAEs occurring in ≥1 patients in Entire ISS Population

SAEs Occurring in ≥ 1 patients											
		Total (N=1,546)		MMS (N=594)		MS (N=991)		Other PEP[1] (N=311)		Placebo (N=589)	
		N	%	N	%	N	%	N	%	N	%
Total SAEs		95	6.1	20	3.4	48	4.8	5	1.3	21	3.4
SOC	**Preferred Term**										
Gastrointestinal	Abdominal pain	7	0.4	1	0.2	5	0.5	0	0	1	0.2
	Vomiting	4	0.3	1	0.2	3	0.3	0	0	0	0
	Nausea	3	0.2	0	0	3	0.3	0	0	0	0
General and administration site	Pyrexia	7	0.5	4	0.7	2	0.2	0	0	1	0.2
Infections and infestations	Bronchitis acute	3	0.2	2	0.3	1	0.1	0	0	0	0
	Pneumonia	8	0.5	1	0.2	6	0.6	0	0	0	0
	Superinfection lung	3	0.2	0	0	0	0	0	0	3	0.5
	Upper respiratory tract infection	1	0.1	0	0	0	0	0	0	0	0
Metabolism and nutrition	Hypoglycemia	5	0.3	0	0	2	0.2	0	0	3	0.5
	Dehydration	3	0.2	0	0	3	0.3	0	0	0	0
Respiratory, thoracic and mediastinal	Cough	3	0.2	3	0.5	0	0	0	0	0	0
	Lung disorder	8	0.5	1	0.2	7	0.7	0	0	0	0
Skin and subcutaneous tissue	Cold sweat	1	0.1	0	0	0	0	0	0	1	0.2

[1] Including Cotazym, Pancrease, Pancrex, and Panzytrat commercial PEPs

Additional analyses of SAEs by this Reviewer by Baseline demographic characteristics for patients in the ISS showed that for patients with CF, male and female patients were approximately equally represented. In the chronic pancreatitis (CP), acute pancreatitis (AP), and pancreatectomy (PY) populations, male to female ratios were about 2 to 1. For CF patients, male and female patients reported any SAE about as frequently. For patients with CP, AP and PY, males as compared to females reported any SAEs in a ratio of approximately 2:1, which reflected gender composition at entry. Thus, no differences by gender were seen in rates of SAE reporting with Creon exposure. There was also no obvious association in rates of SAE reporting by Baseline demographics for race (data not shown).

Thus, this Reviewer concludes that the type and incidence of SAEs reported in the Creon MMS and placebo treatment groups in the ISS are similar.

7.1.2.3 Serious Adverse Events: Pediatric Experience

This Reviewer also assessed the SAE experience of the pediatric sub-population by reviewing adverse event information from the three pediatric CF safety studies, including the Prior Infant CF Safety, Prior Pediatric CF Safety Study, and Prior Young Adult CF Safety Study. It is noted that the AE dataset did distinguish between CFC and MMS treated patients, and SAEs in CFC and MMS treated patients are reported as occurring in MMS treated patients in this discussion and in table 11 below.

SAEs were more commonly reported in pediatric patients treated with Creon MMS (9 of 130 patients; 7%) than patients treated with placebo (2 of 40 patients; 3%). The relevance of this finding is unclear, but may be explained by a greater exposure time of patients to Creon MMS (about 524 patient weeks of exposure) than to placebo (about 60 patient weeks of exposure). The most commonly reported SAEs by SOC overall for all of these pediatric patients were gastrointestinal disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders. By Preferred Term, only lower respiratory tract infection was reported by more than one patient (reported by two patients). These finding findings are summarized in Table 12 as follows.

Table 12: SAEs in the Prior Infant CF Safety Study, Prior Pediatric CF Safety Study, and Prior Young Adult CF Safety Study

Exposure in three Pediatric CF Studies		Total (N=133)		MMS (N=130)		MS (N=93)		Placebo (N=40)	
		N	%	N	%	N	%	N	%
		12	9	9	7	2	2	1	2.5
SOC	Preferred Term								
Gastrointestinal	Abdominal pain upper	1	0.8	0	0	1	0.7	0	0
	Distal intestinal obstruction syndrome	1	0.8	1	0.8	0	0	0	0
	Intussusception	1	0.8	1	0.8	0	0	0	0
	Meconium ileus	1	0.8	1	0.8	0	0	0	0
Infections and infestations	Appendiceal abscess	1	0.8	1	0.8	0	0	0	0
	Acute otitis media	0	0	0	0	0	0	1	2.5
	Lower respiratory tract infection	2	1.6	2	1.6	0	0	0	0
	Lung infection pseudomonal	1	0.8	1	0.8	0	0	0	0
Reproductive system and breast	Testicular torsion	1	0.8	1	0.8	0	0	0	0
Respiratory, thoracic and mediastinal	Bronchial obstruction	1	0.8	1	0.8	0	0	0	0
	Bronchospasm	1	0.8	0	0	1	0.7	0	0
Surgical and medical procedures	Gastrostomy tube insertion	1	0.8	1	0.8	0	0	0	0

Six of 34 patients in study Prior Young Adult CF Safety Study were $\geq$ 18 years of age.

The incidence of SAEs in the pediatric safety studies for patients treated with Creon MMS (7%) is about twice as high as the incidence in placebo-treated patients (3%). The relevance of this finding is unclear, but may be explained by a greater exposure time of patients to Creon MMS (about 524 patient-weeks of exposure) than to placebo (about 60 patient-weeks of exposure). The lower incidence of lower respiratory tract infections in the placebo-treated as compared to Creon MMS-treated patients may also be due to the shorter duration of placebo treatment, and the lower number of placebo treated patients compared to Creon MMS (CMP) treated patients.

In summary, from the results reported in these three studies, SAEs in children with CF treated with Creon MMS are similar in type to SAEs reported in the overall Creon MMS-treated population included in the ISS. The most commonly reported SAEs were gastrointestinal disorders and upper and lower respiratory tract infections, and appear to be consistent with underlying disease. Differences in

incidence rates for SAEs between the Creon MMS-treated and placebo-treated patients were likely attributable to the longer duration of exposure to Creon MMS than to placebo in these studies.

7.1.2.4 Summary Discussion of SAEs

The Serious Adverse Events reported in the ISS were predominantly reported in the System Organ Class categories of (1) general disorders and administration site conditions, (2) gastrointestinal disorders, (3) infections and infestations, and (4) respiratory, thoracic and mediastinal disorders. The most commonly reported SAEs by PT in the Creon MMS group were pyrexia (0.7%), cough (0.5%), and acute bronchitis (0.3%), and the most commonly reported SAEs in the placebo group were superinfection of the lung and hypoglycemia (each in 0.5%). In the opinion of this Reviewer, differences noted between the Creon MMS-treated and placebo-treated groups were minor, and were likely related to underlying diagnoses (e.g. diabetes mellitus).

Thus, in general, the types and frequencies of the reported SAEs in Creon MMS-treated patients are similar to those reported in the placebo-treated patients, and to those SAEs reported during the original NDA review of this product. These findings are generally similar to, and not readily distinguishable from, underlying primary disease or common complications of primary disease.

No SAEs were reported in the New Infant CF Study.

The most commonly reported SAEs (by SOc and PT) from the Prior Infant Safety Study, the Prior Pediatric Safety Study, and Prior Young Adult CF Study (gastrointestinal and respiratory) are similar to the most commonly SAEs reported in the overall ISS population treated with Creon MMS (CMP). In the opinion of this Reviewer, the increased incidence of SAEs in children treated with Creon MMS in the Prior Infant Safety Study, the Prior Pediatric Safety Study, and Prior Young Adult CF Study (7%) compared to all patients in the ISS treated with Creon MMS (CMP) (3%) is not clinically meaningful due to lack of consistent study methods and treatment protocols. This Reviewer concludes that the similarity in types of SAEs reported by Pediatric and Adult is more relevant.

In the New Adult PEI study, three patients experienced SAEs in the placebo run-in phase. Of four patients with SAEs during the DB treatment phase, three patients in the placebo group experienced one SAE each, including pyrexia, subdural hematoma, and hypoglycemia. One patient in the high-dose (3 gram/day) group had pyrexia. No SAEs were attributable to administration of Creon MMS. This Reviewer concludes that SAEs in patients in this study are substantially similar in type to SAEs reported in the ISS.

Thus overall, this Reviewer concludes that in the ISS, in the studies individually reviewed (New Infant CF and Adult PEI studies), and in the pooled assessment of the Pediatric Safety Study experience, the types of SAEs reported appear to be related to entry diagnoses, such as CF, PY, or cancer, or are age-related, such as occult cardiovascular disease in the elderly, and do not appear to be directly attributable to the use of Creon MMS. This Reviewer also concludes that there is no clinically meaningful difference in the types of SAEs reported in children with CF treated with Creon MMS

(CMP) compared to adults with CF treated with Creon MMS or for the entire ISS population treated with Creon MMS (CMP).

7.1.3 Dropouts and Other Significant Adverse Events

Information on patients who withdrew (dropouts) from the studies included in the ISS is followed by data on dropouts from the non-integrated, long-term studies. This Reviewer designated all AEs reported on the day of withdrawal and the reason stated in the accompanying CRF (if available for review) as being temporally associated with the withdrawal. If the reason for withdrawal was not provided in the CRF, if the CRF was not available for review, or if no AE was listed in the AE dataset on the day of withdrawal, AEs listed on the most recent preceding day are designated as being temporally associated with the withdrawal.

7.1.3.1 Profile of Dropouts in the ISS

Throughout all drug phases, including pre-treatment and post-treatment, of 1,546 patients treated with any Creon product, any Other PEP, or placebo, 53 patients (3%) withdrew due to 100 listed AEs. These withdrawals appeared to be evenly distributed across the treatment groups, including 2% of all patients treated with MMS, 2% treated with MS, and 3% treated with Placebo w.0ithdrawing due to AEs. No withdrawals were reported in patients receiving Other PEPs, but as discussed (in the introduction to section 7.1.2 above), methodological issues in studies of Other PEPs prevented a complete assessment of the safety of the Other PEPs.

Withdrawal due to an AE was more common in patients with acute pancreatitis (7% of 77 patients) and in patients with "other diagnoses" (9% of 106 patients), than in patients with CP (3% of 358 patients), CF (2% of 743 patients), post-pancreatic surgery (3% of 153 patients), diabetes mellitus (2% of 109 patients), and HIV (N=1, denominator unavailable). This Reviewer believes the increased incidence of withdrawal in patients with acute pancreatitis compared to withdrawals in patients with CF, CP, and post-pancreatic surgery may be explained by the frequently rapid change in the clinical state of patients with acute pancreatitis compared to patients with chronic pancreatitis and cystic fibrosis.

One additional demographic trend noted by this Reviewer was that in patients who withdrew due to AEs, almost all (98%) of the 53 patients who withdrew were Caucasian, whereas of the entire ISS population, 67% of was Caucasian, 21% was of Unknown race, 4% was of Other race, 7% was Asian, and 2% was Black. There was no obvious explanation for this imbalance, but it is unlikely to be clinically relevant.

No trends by gender were seen for patient withdrawals.

7.1.3.2 Adverse Events Associated with Dropouts

The most commonly reported AEs leading to withdrawal were abdominal pain, diarrhea, nausea, and vomiting (reported by 1% of patients in the ISS, each). The most commonly reported AEs leading to withdrawal in patients treated with Creon MMS were abdominal pain, diarrhea, and nausea (1% each). The most commonly reported AE associated with withdrawal in patients treated with placebo was superinfection of the lung (reported by 2 patients, <1%); the remainder of AEs associated with withdrawal in the placebo-treated group were reported by one patient each. In the opinion of this Reviewer, AEs leading to withdrawal are related to underlying diagnoses, and the differences in AEs leading to withdrawal in the placebo and Creon MMS (CMP) treated groups is not clinically meaningful.

The most commonly reported (by ≥2 patients) AEs leading to withdrawal are summarized in Table 13 below (a table of all AEs leading to withdrawal is located Appendix 10.2 of this review). The table does not include information on three patients who withdrew after screening but before first study dose (placebo or study drug), and does not include AEs which were causally related to death, which are described in section 7.1 of this document.

Table 13: AEs Leading to Withdrawal occurring in ≥2 patients in the ISS

All Patients who dropped out by treatment group		All Patients (N=1,546)		MMS (N=594)		MS (N=991)		Placebo (N=589)	
		N	%	N	%	N	%	N	%
		53	3.4	14	2.4	19	1.9	17	2.9
Listing of Individual AEs									
SOC	Preferred Term	N	%	N	%	N	%	N	%
Cardiac disorders	Cardiac failure	2	0.1	0	0	1	0.1	1	0.2
Gastrointestinal disorders	Abdominal pain	10	0.7	6	1	3	0.3	1	0.2
	Diarrhea	7	0.5	4	0.7	2	0.2	1	0.2
	Nausea	7	0.5	3	0.5	4	0.4	0	0
	Vomiting	7	0.5	2	0.3	4	0.4	1	0.2
	Abdominal pain upper	3	0.2	0	0.0	2	0.2	1	0.2
	Constipation	2	0.1	1	0.2	1	0.1	0	0
	Flatulence	2	0.1	2	0.3	0	0.0	0	0
Infections and infestations	Superinfection lung	2	0.1	0	0	0	0	2	0.3
Metabolism and nutrition disorders	Dehydration	3	0.2	0	0	3	0.3	0	0
	Hypoglycemia	2	0.1	0	0	1	0.1	1	0.2
Musculoskeletal and connective tissue disorders	Muscle spasms	2	0.1	2	0.3	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Cough	2	0.1	2	0.3	0	0	0	0
	Respiratory failure	2	0.1	1	0.2	0	0	1	0.2

In summary, withdrawal due to AEs was most commonly due to gastrointestinal complaints, and was associated with the entry diagnosis of acute pancreatitis, which possibly reflected the natural disease course of these patients. Rates of withdrawal in patients with CF, CP, and diabetes mellitus was approximately equal (2%, 3%, and 2%, respectively, of patients who withdrew had these conditions). Withdrawals were approximately evenly distributed among patients treated with Creon MMS, Creon MS, and placebo. Therefore, this Reviewer concludes that withdrawals due to AEs were most likely

related to underlying disease, and not to treatment, since patients treated with Creon MMS were no more likely to withdraw from treatment due to AEs than were patients treated with placebo.

7.1.3.3 Other significant adverse events

Rare cases of fibrosing colonopathy (FC) have been reported with PEP use, and are thought to be associated with high-dose PEP administration in younger patients. Given the severity of this diagnosis, surveillance for FC in PEP clinical development programs is relevant to the assessment of safety in this class of medications. No instances of fibrosing colonopathy (FC) were reported in the Creon ISS; however, limitations in the safety surveillance program were noted, and conclusive statements regarding the adequacy of FC case detection are not possible for several reasons. First, FC is a histopathologic diagnosis and routine surveillance with colonoscopy and biopsy was not routinely performed in any study. Second, while FC is commonly described as a symptomatically severe and acute process, literature suggests it may have a chronic indolent course; therefore, though severely symptomatic cases might have come to clinical attention during safety assessments, incipient cases might not have been recognized. Third, though fibrosing colonopathy is classically described following high-dose lipase treatment, the doses of Creon MMS administered in the New Infant CF Study, New Adult PEI Study, Prior Pediatric and Adult CF Studies, and the Prior Adult CP Study (e.g., the efficacy trials) were within current guidelines promulgated to decrease the risk of FC. Fourth, though the time of exposure required to develop FC is undetermined, the short duration of most of the studies (two to six weeks) may not have provided a long enough exposure to precipitate FC. Finally, cases of FC in the medical literature appear to have been reported only sporadically. The population studied was relatively small and given the rarity of FC, may not have been large enough to detect an FC safety signal. Therefore, this Reviewer believes that although there were no obvious cases of FC reported in this CR amendment, no conclusions can be drawn regarding the adequacy of FC case detection for the overall ISS population, and monitoring for FC is likely best performed in the post-marketing setting.

Since Creon is an animal-derived protein product, allergy/hypersensitivity reactions are of interest for the assessment of safety of Creon administration. No cases of anaphylaxis were reported in the ISS; however, eleven hypersensitivity events were reported in five patients. The verbatim terms used for the two patients receiving Creon MMS were allergy and allergies (itching of eyes/sneezing). The investigator term used for the one patient receiving Creon MS was allergic reaction. The investigator terms used for the two patients receiving placebo were environmental allergies and allergy. None of the patients withdrew or died due to these events, and only two of the eleven events required treatment. These findings are not unexpected because PEPs act locally in the gut and systemic absorption is minimal, decreasing the likelihood of systemic reactions such as anaphylaxis. The similar rates of hypersensitivity reactions in the Creon MMS and placebo group, and the similar descriptions provided suggest these events were related to environmental allergies. In the opinion of this Reviewer, monitoring for anaphylaxis was felt to be adequate and treatment with Creon MMS (CMP) does not appear to be associated with a high risk of anaphylaxis or other allergic reactions.

Hyperuricemia is associated with the use of all PEPs, and is thought to be related to the purine content of pancreatic extracts from which the PEPs are produced.[4] Thus, monitoring of uric acid levels in the

Creon clinical development program was also felt to be of importance to the overall assessment of safety. Assessment of blood uric acid levels was hampered by a lack of standardized laboratory evaluations across all studies, use of differing units of measure and incorrect units of measure, and frequent errors in transcription of numerical results. Despite these limitations, the following are noted:

- None of the four patients with hyperuricemia events listed in the ISS AE dataset were receiving Creon MMS.
- Uric acid was not assessed in the New Infant CF study.
- Uric acid was assessed in the New Adult PEI study. There was no effect of Creon treatment on blood uric acid noted in this study.
- Uric acid was assessed in the Prior Pediatric CF study. Hyperuricosuria was noted in 5% (2 of 34) patients during treatment with Creon MMS. Both patients had baseline blood uric acid levels near the upper limit of normal. One patient's blood uric acid increased by 1 mg/dL and the other patient's blood uric acid increased by 0.6 mg/dL. The dataset does not indicate if any clinical action was taken. In the 50% of patients randomized to placebo withdrawal, there was no trend toward decrease in blood uric acid when switching from Creon MMS to placebo. The individual study report is not available for review.
- Uric acid was assessed in the Prior Adult CF Study. Hyperuricosuria was seen in 16% (5 of 31) patients treated with Creon MMS. All five patients had baseline blood uric acid levels near the upper limit of normal. One patient's blood uric acid level increase from 3.8 to 7 mg/dL on randomized withdrawal. The dataset does not indicate if any clinical action was taken. In the 50% of patients randomized to placebo withdrawal, there was no trend toward a decrease in blood uric acid when switching from Creon MMS to placebo. The individual study report is not available for review.

In the opinion of this Reviewer, hyperuricemia was associated with Creon MMS treatment in clinical studies. This finding is relevant to patients with the impaired liver function commonly seen in older patients with cystic fibrosis and in patients with chronic pancreatitis. This finding is also relevant in patients with impaired renal function, and impaired uric acid metabolism (e.g. gout). Should Creon receive NDA approval, labeling should address the risk of hyperuricemia associated with Creon administration.

7.1.4 Other Search Strategies

No other search strategies were performed.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse event (AE) collection methods varied between studies and included onsite interviews, review of patient or caregiver diaries, physical examination of the patient, radiological and other procedural test information, and review of clinical laboratory data. AEs were monitored and recorded by

investigators or their designees from the time of study entry (signing of the Informed Consent) and at each study visit through the completion of the studies. Clinically significant worsening from screening in physical examinations, vital signs, and laboratory evaluations were documented as AEs.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The Sponsor reported all AEs in the final ISS (ADV) dataset using Medical Dictionary for Regulatory Activities (MedDRA) SOC and PT terminology. The New Pediatric CF, Prior Pediatric CF, and Prior Adult CF studies, and the New and Prior Adult PEI studies were originally coded using MedDRA, and this Reviewer assesses that the MedDRA SOC and PT coding for these studies was appropriate. Adverse event information from the remaining studies submitted to the ISS was originally coded using either MedDRA or Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). AEs coded in COSTART were converted to MedDRA for incorporation into the ADV dataset. A direct comparison of COSTART and MedDRA terms could not be performed by this Reviewer; however, in studies where COSTART was originally used, comparison of the verbatim terms with corresponding MedDRA terms indicates that MedDRA SOC and PT terms used in ADV appeared generally appropriate.

7.1.5.3 Incidence of Common Adverse Events

This Reviewer constructed incidence rate tables of common AEs from the ISS safety dataset (ADV dataset), which included all AEs in the ISS pooled from the individual studies. AE incidence rates were calculated using all patients who received at least one dose of study medication as the denominator, with recurrent or continuing AEs counted only once. AE incidence rates for each treatment (Creon MMS, Creon MS, Other PEPs, and placebo) were calculated using all patients who received at least one dose of each treatment as the denominator. AEs occurring during the screening/baseline period were reviewed, and only notable AEs occurring during this time period are discussed.

In addition to an assessment of the AEs from all pooled studies reported in the ISS, this Reviewer also analyzed the AEs reported in individual studies, including the New Infant CF Study and the New Adult PEI study, and performed an assessment of the Pediatric CF population AE experience in the pooled AE dataset for the Prior Infant, Pediatric and Young Adult Safety Studies.

Additionally, approximately 1,200 AEs listed in the ADV dataset of the ISS were not classified for seriousness. These AEs were predominantly from studies where the seriousness and severity of AEs were not intended to be assessed. To determine if type or incidence of AEs in this group differed from type and incidence of AEs reported in the overall ISS, this Reviewer assessed type and incidence of AEs with unknown seriousness. The denominator population was empirically assigned as the denominator of the total population of all studies where at least one patient had an AE of unknown seriousness. Type and incidence of AEs of unknown seriousness conclude this section.

Assessment of Common Adverse Events

Common AEs in the Prior Infant CF Safety Study, Prior Pediatric CF Safety Study, and Prior Young Adult CF Safety Study

The assessment of the AEs in the pooled analysis of the three pediatric CF safety studies (Prior Infant, Pediatric, and Young Adult CF Safety Studies) was limited by the finding that the Sponsor did not use uniform treatments, blinding, and controls in these studies. Thus, the objective assessment of causality of the commonly reported AE was felt to be impaired.

In the pooled analysis of these three studies, AEs were reported in 61% of the 133 patients treated with Creon MMS and in 15% of the 40 patients treated with placebo. The most common AEs reported in patients treated with Creon MMS were headache (43%), cough (34%), abdominal pain (20%), and lower respiratory tract infection (17%). The most common AEs reported in patients treated with placebo were nasopharyngitis (5%), bronchitis (3%), and bronchial obstruction (35%). These AEs are similar to common complaints reported in children with CF and are similar in type to common AEs reported in the ISS in all patients treated with Creon MMS. Due to differences in study designs (e.g., two of the studies were open label) and since placebo control was only provided to 40 of 134 patients (30%), the differences in types and frequencies of AEs between the placebo and Creon MMS groups are likely not clinically meaningful, and definitive statements regarding causality cannot be made. These findings are summarized in Table 14 in section 7.1.5.4 below.

Common AEs in the New Infant CF Study
In the New Infant CF Study, three AEs were reported in two patients during the Baseline period. One patient had malnutrition and cow's milk intolerance, and one patient had meteorism. There were 21 non-serious AEs reported during treatment with Creon MMS. The most common AEs reported during Creon treatment were pyrexia (33%), cough (25%), constipation (17%), and respiratory tract infections (17%). Conjunctivitis, abdominal pain NOS, viral infection NOS, nasopharyngitis, gastroenteritis adenovirus, rhinitis NOS, and pharyngeal pain each occurred in 8% of the study population. These findings are similar to common presenting complaints in healthy infants and infants with CF. The increased incidence of AEs during double-blind treatment compared to the Baseline phase is likely due to the short Baseline period (seven to ten days) compared to the treatment period (eight weeks). This Reviewer concludes that the AE results in this study can be used in labeling to describe safety of Creon MMS (CMP) in infants with CF from one to 24 months of age.

Common AEs in the New Adult PEI Study
In the New Adult PEI study, 45 patients experienced an AE during the placebo run-in period. The most common AEs during the placebo run-in period were diarrhea (9% of patients), hypoglycemia (7%), and abdominal distension, loose stools, and abnormalities of alanine aminotransferase and aspartic acid aminotransferase (5% each). AEs during the placebo run-in period were less common in the group randomized to placebo during double-blind treatment (40% of patients in the placebo group, 52% of patients the low-dose group, and 52% of patients in the high-dose group).

During the treatment phase, 64 of 94 patients reporting at least one AE, including 63% of patients in the placebo group, 70% in the high-dose group, and 74% in the low-dose group. The lower incidence

of AEs in the group randomized to placebo during double-blind treatment is similar in magnitude to the lower rate of AEs in the placebo group noted during the single-blind placebo treatment phase. Review of the study report and case report forms (CRFs) was not helpful in determining why AEs were less common in the placebo group during the single-blind and double-blind phases.

The most common AEs reported by patients overall (placebo, low-dose Creon MMS, or high-dose Creon MMS) during the DB treatment period were abdominal pain (10%), constipation (9%), and abdominal distension, diarrhea, and malaise (7% each). The most common AEs in the placebo group were malaise (14%), abdominal pain, abdominal distension, and hypoglycemia (10% each). The most common AEs in the low-dose group were abdominal pain, back pain, and headache (10% each). The most common AEs in the high-dose group were constipation and diarrhea (15% each), followed by abdominal pain, vomiting, and gastrointestinal upset (9% each).

This Reviewer concludes that the AEs reported in the placebo and Creon treatment groups reflect underlying pathophysiology, and although some differences in types and frequencies of AEs were noted between the treatment groups, these differences were felt to be minor. In the opinion of this Reviewer, the treatment of adult patients with PEI due to PY and CP with Creon MMS does not appear to be associated with an obvious safety signal for AEs, and most AEs were intolerances noted predominantly in the Gastrointestinal system. This safety information is similar to the AE profile of Creon noted in previous studies and in the medical literature with Creon (and other PEPs), and is adequate to inform the labeling of Creon MMS (CMP) in patients with PEI due to PY and CP. These findings are summarized in Table 15 in section 7.1.5.4 of this review.

Common AEs in the ISS

This Reviewer defined AEs as events in the ADV dataset that occurred during treatment (drug or placebo treatment), inter-period drug holidays and run-in phases, or within 14 days of last drug or placebo dose. This analysis identified 3,766 non-serious events in 1,011 patients in the ISS safety dataset, including events of unknown seriousness. The Sponsor used a similar strategy, but used the EXTADV dataset and included events within 10 days of last dose, which yielded 3,621 non-serious events occurring in 983 patients. The greater number of patients and AEs derived with the ADV dataset is explained by including four more days of post-treatment events, all inter-period drug holiday events, and run-in phase AEs. Overall, there is no clinically meaningful differences seen between the two analyses performed (by the Sponsor and by this Reviewer), and the following results are summarized from this Reviewer's analysis of common AEs reported in the ISS.

AEs were reported in 65% of all patients included in the ISS, including in 61% of patients treated with Creon MMS, 47% of patients treated with Creon MS, 49% of patients treated with Other PEPs, and 49% of placebo-treated patients.

The most common AEs reported overall were abdominal pain (16% of all patients), headache (14%), diarrhea (9%), cough (7%), and vomiting (7%). The most common AEs reported in the placebo-treated groups were abdominal pain (9%), diarrhea and headache (8% each), and nausea and flatulence (4% each). The most common AEs reported in the Creon CMP (MMS) group were headache (12%), abdominal pain (9%), cough (8%), and diarrhea (7%). The most common adverse events reported in the Creon MS group were abdominal pain (10%), headache (9%), and cough (7%). The most common

AEs reported in the Other PEP group were abdominal pain (10% of patients) and diarrhea (7%), followed by vomiting and cough (5% each). These adverse events reflect the underlying disease processes (e.g., PEI due to CF or PY), and were similar across treatment groups. These findings are summarized in Table 16 in section 7.1.5.4 of this review.

Common AEs in the ISS where seriousness is unknown

To calculate incidence for the population of patients where seriousness was not assessed, this Reviewer defined the denominator as the total population of all studies where at least one patient had an AE of unknown seriousness. Of the population so defined, AEs occurred in 46% of all patients, 52% of patients treated with Creon MS, 59% of patients treated with Other PEPs, and 16% of patients treated with Placebo. No patients in this population were treated with Creon MMS, and there are no instances in the ADV dataset where patients treated with Creon MMS had AEs of unknown seriousness or severity.

The most common AEs of unknown seriousness were abdominal pain (14% of patients), cough (12%), diarrhea (9%), and vomiting (9%). The most common AEs of unknown seriousness in patients receiving placebo were nausea (3%), and vomiting, diarrhea, "pain not otherwise specified", and headache (2%, each). The most common AEs of unknown seriousness in patients receiving Creon MS were abdominal pain (12%), cough (13%), diarrhea (8%), and vomiting (7%). The most common AEs of unknown seriousness in patients receiving Other PEPs were abdominal pain (23%), abnormal feces (21%), diarrhea (18%), vomiting (16%), headache (13%), and cough (11%).

The types of common AEs reported in the population where seriousness of AEs was not assessed were similar to the types of AEs reported in the entire ISS population, and AEs reflect complaints related to underlying diseases. The lower incidence of AEs in patients treated with placebo cannot be readily explained; however, may be partly accounted for by differences in study designs (e.g., open-label and blinded study designs included in the analysis).

This Reviewer concludes that the lack of assessment of seriousness should not prohibit drawing conclusions on the safety of Creon MMS (CMP), because all Creon MMS treatments and 90% of placebo treatments were provided in studies where AE seriousness was evaluated. These findings are summarized in Table 57 in Appendix 10.1.5 of this review.

7.1.5.4 Common adverse event tables

Table 14 below displays AEs occurring in 3% or greater of patients in the three pooled pediatric CF safety studies (Prior Infant CF Safety Study, Prior Pediatric CF Safety Study, and Prior Young Adult CF Safety Study) discussed in section 7.1.5.3 above.

Table 14: AEs reported in ≥3% of Patients in Three Pooled Pediatric Cystic Fibrosis Studies[1]

Exposure in three Pediatric CF Studies		Total Patients (N=133)		Creon MMS (N=130)		Creon MS (N=93)		Placebo (N=40)	
		N	%	N	%	N	%	N	%
		81	61	73	55			6	15
SOC	Preferred Term								
Ear and labyrinth	Ear pain	4	3	1	1	3	3	0	0
Gastrointestinal	Abdominal pain	27	20	11	8	16	17	0	0
	Vomiting	14	11	11	8	3	3	0	0
	Abdominal pain upper	10	8	6	5	4	4	0	0
	Nausea	8	6	6	5	2	2	0	0
	Diarrhea	6	5	5	4	1	1	0	0
	Toothache	6	5	4	3	2	2	0	0
	Constipation	5	4	3	2	2	2	0	0
	Distal intestinal obstruction syndrome	4	3	3	2	1	1	0	0
General and administration site	Pyrexia	8	6	4	3	4	4	0	0
Infections and infestations	Lower respiratory tract infection	23	17	11	8	12	13	0	0
	Nasopharyngitis	13	10	5	4	6	6	2	5
	Bronchitis	6	5	5	4	0	0	1	3
Musculoskeletal and connective tissue	Arthralgia	4	3	2	2	2	2	0	0
Nervous system	Headache	57	43	17	13	40	43	0	0
Respiratory, thoracic and mediastinal	Cough	45	34	18	14	27	29	0	0
	Pharyngolaryngeal pain	5	4	0	0	5	5	0	0
	Bronchial obstruction	4	3	3	2	0	0	1	3

[1] Prior Infant CF Safety Study, Prior Pediatric CF Safety Study, and Prior Young Adult CF Safety Study

Table 15 below displays AEs occurring in 3% or greater of patients in the New Adult PEI Study, discussed in section 7.1.5.3 above.

Table 15: New Adult PEI Study, AEs reported ≥ 3% of Patients

All patients by treatment group		Total (N=94)			1.5 g/day (N=31)			3 g/day (N=33)			Placebo (N=30)		
		AEs	N	%	AE	N	%	AE	N	%	AE	N	%
		158	65	69	41	23	74	63	23	70	54	19	63
Listing of Individual AEs													
SOC	Preferred Term	AEs	N	%	AE	N	%	AE	N	%	AE	N	%
Gastrointestinal	Abdominal pain NOS	9	9	10	3	3	10	3	3	9	3	3	10
	Abdominal distension	8	7	7	3	2	7	2	2	6	3	3	10
	Constipation	8	8	9	1	1	3	5	5	15	2	2	7
	Diarrhea NOS	7	7	7	0	0	0	5	5	15	2	2	7
	Loose stools	6	6	6	2	2	7	2	2	6	2	2	7
	Vomiting NOS	4	4	4	1	1	3	3	3	9	0	0	0
	Gastrointestinal upset	3	3	3	0	0	0	3	3	9	0	0	0
General disorders and administration site conditions	Malaise	7	7	7	1	1	3	2	2	6	4	4	13
	Chest discomfort	3	3	3	0	0	0	1	1	3	2	2	7
Investigations	Blood glucose increased	6	6	6	1	1	3	3	3	9	2	2	7
	Glucose urine present	3	3	3	2	2	7	0	0	0	1	1	3
Metabolism and nutrition	Hypoglycemia NOS	4	4	4	0	0	0	1	1	3	3	3	10
Musculoskeletal and connective tissue	Back pain	4	4	4	3	3	10	1	1	3	0	0	0
Nervous system	Headache	4	4	4	3	3	10	1	1	3	0	0	0
	Dizziness	3	3	3	0	0	0	1	1	3	2	2	7
Skin and subcutaneous tissue	Cold sweat	3	3	3	0	0	0	2	2	6	1	1	3
	Pruritus	3	3	3	2	2	7	0	0	0	1	1	3

Table 16 below displays AEs occurring in 1% or greater of patients in all studies reported in the ISS, discussed in section 7.1.5.3 above. This table includes AEs reported during treatment with any drug or placebo, and events within 14 days of most recent dose. This table does not include events that were classified as pre-treatment (for example, events which occurred between obtaining informed consent, but prior to randomization, are not included).

Table 16: AEs occurring in 1% or greater of patients in ISS studies [1, 2, 3]

All AEs in ISS		Total (N=1546)		MMS (N=594)		MS (N=991)		Other PEPs (N= 311)		Placebo (N=589)	
		N	%	N	%	N	%	N	%	N	%
		1011	65	363	61	470	47	153	49	291	49
AEs in ≥ 1% of patients in any treatment group											
SOC	Preferred Term										
Blood and lymphatic system	Anemia	15	1	3	1	6	1	3	1	2	0
Gastrointestinal	Abdominal pain	241	16	54	9	102	10	32	10	53	9
	Diarrhea	143	9	39	7	39	4	21	7	44	8
	Vomiting	109	7	35	6	43	4	16	5	15	3
	Nausea	92	6	25	4	35	4	8	3	24	4
	Abdominal pain upper	65	4	21	4	22	2	8	3	14	3
	Flatulence	72	5	16	3	25	3	8	3	23	4
	Constipation	54	4	21	4	15	2	8	3	10	2
	Abnormal feces	32	2	1	0	17	2	13	4	1	0
	Dyspepsia	32	2	15	3	3	0	1	0	13	2
	Abdominal distension	38	3	9	2	11	1	6	2	12	2
General and administration site	Pyrexia	77	5	20	3	36	4	13	4	8	1
	Fatigue	29	2	12	2	6	1	3	1	8	1
	Malaise	28	2	7	1	10	1	4	1	7	1
	Pain	25	2	6	1	12	1	3	1	4	1
	Chest pain*	13	1	6	1	5	1	0	0	2	0
	Edema peripheral*	11	1	2	0	3	0	0	0	6	1
Hepatobiliary	Hepatic function abnormal	44	3	6	1	17	2	7	2	14	2
Infections and infestations	Nasopharyngitis	63	4	24	4	26	3	3	1	9	2
	Lower respiratory tract infection	32	2	9	2	20	2	3	1	0	0
	Rhinitis	34	2	8	1	17	2	6	2	3	1
	Upper respiratory tract infection	28	2	6	1	12	1	7	2	3	1
	Influenza	29	2	7	1	12	1	1	0	9	2
	Bronchitis	22	1	13	2	5	1	2	1	2	0
	Infection	16	1	2	0	12	1	2	1	0	0
Metabolism and nutrition	Hyperglycemia	41	3	9	1	17	2	4	1.3	11	2
	Anorexia	29	2	3	0	12	1	9	3	5	1
	Hypoglycemia	32	2	4	1	8	1	0	0	19	3
	Decreased appetite	18	1	7	1	8	1	1	0	2	0
	Iron deficiency	16	1	0	0	8	1	8	3	0	0

Table 16: AEs occurring in 1% or greater of patients in ISS studies [1, 2, 3]

All AEs in ISS		Total (N=1546)		MMS (N=594)		MS (N=991)		Other PEPs (N= 311)		Placebo (N=589)	
		N	%	N	%	N	%	N	%	N	%
		1011	65	363	61	470	47	153	49	291	49
AEs in ≥ 1% of patients in any treatment group											
SOC	Preferred Term										
Musculoskeletal and connective tissue	Back pain	37	2	13	2	13	1	2	1	9	2
	Arthralgia	21	1	6	1	6	1	2	1	7	1
	Pain in extremity*	11	1	3	1	1	0	0	0	7	1
	Shoulder pain*	12	1	5	1	1	0	0	0	6	1
Nervous system	Headache	208	14	72	12	91	9	8	3	36	6
	Dizziness	22	1	6	1	6	1	0	0	10	2
Psychiatric	Insomnia*	12	1	1	0	1	0	4	1	6	1
Renal and urinary	Glycosuria*	12	1	3	1	5	1	3	1	1	0
Respiratory, thoracic and mediastinal	Cough	131	9	47	8	65	7	14	5	4	1
	Pharyngolaryngeal pain	39	3	15	3	14	1	4	1	6	1
	Productive cough	22	1	7	1	11	1	3	1	1	0
	Lung disorder	38	3	11	2	13	1	10	3	3	1
Skin and subcutaneous tissue	Rash	21	1	6	1	11	1	0	0	4	1
	Pruritus	17	1	5	1	3	0	1	0	8	1

[1]AE=Non serious AEs and AEs of unknown seriousness
[2] N=Number of persons experiencing events.
[3]The table does not include six patients with seven post-treatment AEs > 14 days after last dose; includes one event each of epistaxis, cough, lung disorder, headache, hypoglycemia, nasopharyngitis, and anemia.
* AE ≥ 1% in subgroup

7.1.5.5 Identifying common and drug-related adverse events

The method for determining AEs, SAEs, withdrawals, and deaths has been delineated in sections 7.1 through 7.1.5.3 of this review.

Hyperuricemia has been reported in patients taking PEPs[4]. The assessment of hyperuricemia is discussed in section 7.1.3.3 of this review.

7.1.5.6 Additional analyses and explorations

Since pediatric patients with CF are an important treatment population for the PEPs, this Reviewer performed additional analyses to assess the safety of Creon administration to pediatric CF patients. The analyses performed and the results of these analyses are discussed in Sections 7.1, 7.1.2.3, 7.1.2.4, and 7.1.5.3 of this review.

7.1.6 Less Common Adverse Events

Anaphylaxis and allergic/hypersensitivity reactions are discussed in Section 7.1.3.3 of this review.

Fibrosing colonopathy (FC) has been reported in patients taking PEPs, and is thought to be related to high or inappropriate dosing of PEPS, especially in young children. Reports of FC in the literature have been noted to decrease since the publication of dosing guidelines in the 1990's.[6] No cases of FC were reported in the ISS safety update. Assessment of the safety database for FC is discussed in section 7.1.3.3 of this review.

Distal intestinal outlet obstructive syndrome (DIOS) and bowel obstruction are reported in children and adults with CF. Intestinal obstruction was reported in two children with CF in the ISS, neither of whom received Creon MMS. Thus, no relationship of these two events to Creon MMS can be construed since neither patient received the drug.

No other notable less common Adverse Events were noted in the review of the safety dataset submitted in the CR amendment.

7.1.7 Laboratory Findings

All of the clinical studies included in the ISS had the collection and evaluation of laboratory data as part of their protocols. Testing procedures for biochemical, hematological, and urinary parameters varied by individual study protocol. Clinically significant laboratory abnormalities that qualified as AEs are included in the AE datasets and are reported in AE tables.

The laboratory data from studies the New Infant CF Study and the New Adult PEI study were reviewed in depth. The findings by this Reviewer and the Sponsor were identical. Pertinent positive and negative findings are presented below (please also refer to the individual study reports in appendices 10.1.1 and 10.1.2 for full descriptions).

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<u>New Infant CF Study</u>

As expected, decreased concentrations of vitamins A and E were noted at Baseline. There was a slight increase in mean values of vitamins A and E during the study, but mean values remained either below normal or at the lower range of normal for these two analytes. However, clinically meaningful decreases in vitamin E levels were seen in two patients. Marked improvement in vitamins A and E would not be expected due to the short duration of the study.

Also, mean serum cholesterol increased by 0.27 millimol/L, which may be expected with increased lipid absorption with treatment and attendant increase in cholesterol biosynthesis. There were no other notable laboratory findings.

<u>New Adult PEI Study</u>
Notable laboratory findings include:

Clinically meaningful laboratory findings were limited to hyper- or hypoglycemia, and 10 of 11 of the patients with hyper- or hypoglycemia had pre-existing diabetes mellitus. No association with Creon MMS (CMP) treatment was suspected. No other clinically meaningful trends were seen in any other laboratory parameters within or between treatment groups.

Laboratory Findings in the ISS

This Reviewer attempted to assess the potential effect of Creon MMS on blood uric acid; however, several issues hampered review including inconsistent use of units of measure, multiple errors in the dataset (e.g. physiologically impossible uric acid values), lack of uniform laboratory screening procedures, and incomplete drug or placebo treatment information at the time of laboratory assessments.

Assignation of drug or placebo treatment at time of laboratory analysis was performed by this Reviewer by matching protocol name, unique patient identifier, and date from laboratory dataset with the corresponding information in the medication dosing (MEDDOS) dataset.

Blood uric acid levels were recorded for 1,217 patients in 36 studies. There were 279 instances where apparently non-physiologic uric acid levels were due to a conversion errors between micromol/L and millimol/L. This presumed error was corrected and all values were converted to conventional units (mg/dL) for ease of review. While there were no meaningful differences between the Creon MMS and placebo groups at Baseline or during treatment, these findings may not be valid due to the limitations described above. The overall findings of the mean blood uric acid levels by treatment group at Baseline and during treatment are summarized in Table 17 below.

Table 17: Blood uric acid level in 1,009 patients with non-treatment (e.g., Baseline) and phase 1 (drug or placebo) blood uric acid values

N=1,009 [1]	**Creon MMS** N=352			**Creon MS** N=316			**Other PEP** N=65			**Placebo** N=276		
	BSL[2]	Treat[3]	Change	BSL	Treat	Change	BSL	Treat	Change	BSL	Treat	Change
Mean	4.5	4.8	0.3	4.6	4.7	0.1	4.4	4.4	0	4.3	4.5	0.2
SD	1.5	1.4	0.9	1.5	1.4	1.0	1.4	1.4	1.2	1.4	1.2	0.9

[1] Total patients with baseline and phase 1 blood uric acid values=1009
[2] Baseline blood uric acid level
[3] Treatment period blood uric acid level
Total patients with uric acid values measured one or more times=1217 (not shown)

Because patients with PEI due to CF and CP frequently have concomitant alterations in liver function, a review of laboratory abnormalities reported in the ADV AE dataset for alterations in aspartic acid and alanine aminotransferases was performed, which did not reveal any clinically meaningful differences in these analytes between patients treated with Creon MMS (CMP) and patients treated with placebo. No other noteworthy trends in laboratory findings were reported by the Sponsor or noted by this Reviewer.

7.1.8 Vital Signs

Vital signs assessments were performed according to individual study schedules. Clinically significant worsening of vital signs were documented as AEs and were considered in the overall AE assessment above. No notable, relevant, or remarkable trends in vital signs were seen.

Vital signs for the New Infant CF and New Adult PEI studies were thoroughly reviewed by this Reviewer. In the New Infant CF study, except for fevers recorded as AEs, there were no notable abnormal findings. In the New Adult PEI study, there were no clinically meaningful trends in vital signs seen within or between treatment groups compared to Baseline.

7.1.9 Electrocardiograms (ECGs)

Creon is not systemically absorbed and electrocardiogram evaluation was not part of the Creon clinical development program.

7.1.10 Immunogenicity

Creon and other porcine-derived PEPs are not systemically absorbed, and immunogenicity testing was not performed as part of the Creon clinical development program (e.g., anti-enzyme serum immunoglobulin measurements for individual components of Creon, such as lipase, were not assessed).

7.1.11 Human Carcinogenicity

Creon and other porcine-derived PEPs are not systemically absorbed and human carcinogenicity studies were not part of the Creon clinical development program, and no non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA.

A separate O-phthalic acid study report (S0010.7.637.X) was submitted in the NDA CR amendment. Notable issues identified by Dr. Joseph regarding the toxicology studies and the O-phthalic acid study report on 14-June-2007 are that "based on results of the submitted 4-week oral toxicity study of o-phthalic acid in dogs, the 2-year carcinogenicity studies of phthalic anhydride in rats and mice, and other preclinical studies of o-phthalic acid, p-phthalic acid, and phthalic anhydride, the estimated maximum dose of o-phthalic acid resulting from Creon® administration is not considered to be a safety concern."

7.1.12 Special Safety Studies

No special safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No withdrawal or abuse potential is known or suspected with this class of drugs.

7.1.14 Human Reproduction and Pregnancy Data

No studies with Creon MMS were conducted in pregnant women.

It is likely that Creon products will be used by pregnant women and women of reproductive potential. Future labeling should address safety in pregnancy. The Pharmaco-Toxicology review team recommends Pregnancy "Category C"; studies not conducted. This Reviewer concurs with this recommendation.

7.1.15 Assessment of Effect on Growth

The New Infant CF study assessed changes in body mass index (BMI) and weight for height ratio as secondary efficacy parameters. BMI increased from 15.6 (SD 1.7) to 16.3 (SD 1) during the study for a mean increase of 0.7 (SD 1.2; 95% C.I. -1, 1.5). Weight for height ratio showed a mean increase of from 96.8 to 98.8 for mean increase of 2 (SD 6.5; 95% C.I. -2.5, 6.5). The results do not indicate a statistically significant effect on these two growth parameters. Failure to demonstrate an increase in BMI and weight for height in this study occurred because review of the dataset and study report indicates that patients were healthy and not growth deficient at the beginning of the study; therefore, improvement in BMI and weight for height were not expected.

PEPs are widely recognized as having a positive effect on pediatric growth.[1, 2] Studies performed in the Creon clinical development program were, for the most part, short-term studies where long-term growth and development were not assessed, which is consistent with the recommendations for study designs in the Guidance for submitting PEP NDAs. Thus, no formal assessment of pediatric growth and development was expected in the CR amendment.

7.1.16 Overdose Experience

PEPs are not systemically absorbed. An important safety issue regarding PEP use is fibrosing colonopathy (FC). The etiology of FC has not been definitively established, but is thought to be associated with high dose lipase exposure, although some reports indicate the risk of FC is associated with the excipients.[1,5, 6] In order to optimize therapy while minimizing the risk of FC, the Cystic Fibrosis Foundation (CFF), in conjunction with the FDA, recommends starting lipase doses according to age as described below.

The CFF recommends the following dose schedule for full meals:

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.
- Children $\leq$4 years old eating soft or solid foods: begin with 1,000 USP lipase units/kg/meal.
- Children >4 years old: begin with 500 lipase units/kg/meal.
- Doses in excess of 2,500 USP lipase units/kg/meal should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to significantly improve a documented low coefficient of fat absorption.

- The recommended per meal dose should be halved when ingesting snacks.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with fibrosing colonopathy.

The Sponsor's proposed label is unclear. (b) (4) These recommendations should be reflected prominently and accurately in future labeling. Since adoption of the above dosing guidelines, the number of cases of fibrosing colonopathy reported has decreased markedly.

7.1.17 Postmarketing Experience

Creon to-be-marketed-product (TbMP) is not a marketed product, and, therefore, there is no post-marketing experience with the Creon TbMP. The following comments on post-marketing experience refer to Creon currently-marketed-product (CMP) and Creon Microspheres (Creon MS; no longer marketed).

Enteric-coated Creon MS were introduced in Germany in 1982 and Creon MMS debuted in 1993. Creon MS was replaced in the Rest of the World (ROW; includes all countries where Creon is marketed, except the US) by Creon MMS in 2003. The Sponsor states that as of 28-August-2006, marketing authorization for Creon MMS had been granted in 70 non-US countries. As of the date of submission of this NDA update, no Creon MMS product had been withdrawn for safety concerns.

Non-US formulations were marketed as: Creon (Pancrelipase) minimicrospheres, Creon (Pancreatin), Kreon (Pancreatin), Pankreon (Pancreatin), Pankreon forte (Pancreatin), Pankerozym (Pancreatin), Pancrin (Pancreatin), and Papin (Pancreatin). The Sponsor provided a list of 491 post-marketing adverse drug reaction reports associated with different strengths of the different products used by 242 unique foreign and domestic patients. The period of reporting was 01-October-2001 through 20-June-2006.

Deaths and AEs from the post-marketing experience are presented descriptively. Incidence rates of deaths and AEs in the post-marketing experience cannot be determined because the number of exposed patients (the denominator population) is unknown. The Sponsor states 491 post-marketing adverse drug reaction (ADR) reports were received which described events in 242 individuals. No deaths or AEs in the post-marketing experience were reported in the ISS.

Two deaths were reported from the Creon post-marketing experience, as follows:

Report PANC00302001564 is of a 40 year old man with acute gastro-intestinal hemorrhage without stated cause who died from the hemorrhage. The report stated the relationship to Creon products was unlikely.

Report PANC00305002403 is of a 62 year old man who died due to apparent streptococcal-associated necrotizing fasciitis, septic shock, and multiple organ failure while being treated with pancreatin, paracetamol, labetolol hydrochloride, omeprazole, glimepiride, and ibuprofen. Interventions included

multiple antibiotics, ventilation and hemofiltration. The report stated the relationship to Creon products was unlikely.

Gastrointestinal disorders were noted in 41% of post-marketing reports. Other common complaints were skin and subcutaneous tissue disorders (10% of reports), investigations (7% of reports), nervous system disorders (5% or reports), and immune system disorders (2% of reports). The types of AEs reported in post-marketing reports are similar to the types AEs reported in the ISS.

For the MedDRA terms possibly related to fibrosing colonopathy, there was one report each of fibrosing colonopathy, intestinal obstruction, and colitis, which are summarized as follows:

US-SOLVAY-00202000885 reports a 54 year old man with history of pancreatitis who was hospitalized for small intestinal obstruction while taking pancreatin for an unknown period. The patient recovered spontaneously and the relationship to Creon was assessed as possible.

DE-SOLVAY-00305002526 reports a 40 year old woman with nine-day history of recurring diarrhea and tenesmus, and prior medical history of diabetes mellitus, hypertension, hypothyroidism, irritable bowel syndrome, colitis, reflux esophagitis, lactose intolerance, pulmonary embolism, cholecystectomy, appendectomy, hysterectomy, splenectomy, and gastric ulcer. She was being treated with pancreatin. During the hospitalization for the current event, an ileocolonoscopy was performed and showed segmental inflammation in the right colon. She recovered completely and the relationship to Creon products was assessed as unlikely.

US-SOLVAY-00204003851 reports a 25 year old man with cystic fibrosis who had histologically confirmed fibrosing colonopathy. He used multiple PEP products until age 22 years. He was exposed to “Creon 25” for ten months at age 16 years, and continued exposure to other pancreatin products (commercial name not provided) up to age 22 years. The type of PEP and daily lipase unit dose for the intervening period was not reported. The relationship to Creon was assessed as unlikely.

The assessment that the case of FC reported in US-SOLVAY-00204003851 was not related to Creon 25 can not be made from the information provided. Without knowledge of daily lipase dose exposure of any Creon product in the intervening period, the relationship is unknown and ranges from unlikely to probable.

This Reviewer concludes the two post-marketing reported deaths appear related to underlying disease and co-morbidities and do not appear attributable to administration of Creon MMS (CMP). The AEs reported in the post-marketing experience are generally attributable to underlying diseases such as cystic fibrosis and chronic pancreatitis, or unrelated co-morbidities such as cardiovascular disease in the elderly, and do not appear to be causally related to administration of Creon MMS (CMP).

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The description of the Creon primary clinical data sources, clinical development program, patient exposure, and assessments used to evaluate safety are described in detail in the following sections: 1) Section 4 Data Sources, Review Strategy, and Data Integrity; 2) Section 6 Integrated Review of Efficacy; and 3) Section 7 Integrated Review of Safety. Please refer to these sections for additional information.

Safety information was submitted from 57 clinical studies performed between July 1985 and May 2006. Seven studies were not incorporated into the ISS due to data quality issues including inconsistent blinding procedures and lack of study controls, and these studies were not reviewed for safety or efficacy. Sufficient information was provided to allow review of the safety information from the 50 studies in the ISS. The 50 studies in the ISS enrolled a total of 1,546 patients. Of these patients, 743 had cystic fibrosis, 358 had chronic pancreatitis, 153 had pancreatectomy, 109 had diabetes mellitus, 77 had acute pancreatitis, and 109 had other diagnoses. Studies included infants, children, and adults with cystic fibrosis, and adults with chronic pancreatitis and pancreatectomy.

Five trials were analyzed for short-term efficacy and safety. Three trials were performed in patients with cystic fibrosis, including two randomized, double-blind, placebo-controlled trials, and one open-label trial. Two trials were performed in chronic pancreatitis patients, one of which included patients who had undergone pancreatectomy. Both trials were double-blind, placebo-control studies. Original reviews were performed on the New Infant CF and New Adult PEI studies. The Prior Pediatric and Prior Adult CF studies and the Prior Adult CP study were reviewed by Dr. Fathia Gibril during the original review of this NDA (03-December, 2003). Summary comments from Dr. Gibril's review were presented in this review.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary sources of safety information were submitted for review in this CR Amendment.

7.2.3 Adequacy of Overall Clinical Experience

No clinical efficacy and safety studies with Creon to-be marketed product (TbMP) have been performed to date. With the exception of single-dose Creon TbMP exposure in nine patients in the Bridging study, exposure to Creon in the Creon clinical development program has been entirely with Creon CMP or other formulations of Creon that are no longer marketed. Information on exposure to Creon CMP that was submitted to the CR amendment is summarized as follows:

Patients in the ISS may have been exposed to one or more treatments (i.e., Creon MMS, Creon MS, Other PEPs, or placebo). Of 1,546 patients in the ISS, 594 (38%) were exposed to Creon MMS (CMP). Fifty-nine percent (59%) of patients enrolled in CF studies were exposed to Creon MMS;

14% of patients enrolled in CP studies were exposed to Creon MMS; 11% of patients enrolled in post-pancreatic surgery studies were exposed to Creon MMS; and 16% of patients with other primary disorders were exposed to Creon MMS. Eight percent (8%) of patients enrolled in CF studies were exposed to placebo; 54% of patients enrolled in CP studies were exposed to placebo; 13% of patients enrolled in post-pancreatic surgery studies were exposed to placebo; and 26% of patients with other primary disorders were exposed to Creon MMS. These findings are summarized in Table 18 below.

Table 18: Exposure to Treatment Classified by Primary Disease

Studies by Disease Category	Total (N=1546)	Creon MMS (N=594)	Creon MS (N=991)	Other PEP (N=331)	Placebo (N=589)
Cystic Fibrosis, n (%)	743 (48)	351 (59)	574 (58)	277 (90)	49 (8)
Chronic Pancreatitis, n (%)	358 (23)	80 (14)	278 (28)	34 (11)	315 (54)
Post-Pancreatic Surgery[1], n (%)	153 (10)	65 (11)	92 (9)	0 (0)	78 (13)
Diabetes Mellitus, n (%)	109 (7)	55 (9)	0 (0)	0 (0)	54 (9)
Acute Pancreatitis, n (%)	77 (5)	37 (6)	0 (0)	0 (0)	40 (7)
Other[2], n (%)	106 (7)	6 (1)	47 (5)	0 (0)	53 (9)

[1]Pancreatectomy, Gastrectomy [2]HIV, chronic malnutrition

In this Reviewer's opinion, there was adequate exposure of patients with PEI due to CF and other causes (such as CP and post-pancreatic surgery) to Creon MMS and placebo to permit an assessment of the safety of Creon CMP.

For patients included in the ISS, exposure to Creon MMS (CMP) by gender was 64% male and 36% female. The age range of patients exposed to CMP was from one month to 80 years old. Exposure to Creon MMS by race was 70% Caucasian, 11% Asian, 12% where race was categorized as Unknown, 6% where race was categorized as Other (6%), 2% Black, and 0.2% Hispanic. There was a similar Baseline demographic profile for patients exposed to placebo in clinical studies. These findings are summarized in table 19 below (electronically reproduced from Sponsor's table 8.8.8 Volume 26, page 9508).

Table 19: Demographic profile of all patients in ISS

Demographic profile of all patients in ISS	Total	Creon MMS	Creon MS	Other PEP	Placebo
All Patients	1,546	594	991	331	589
Gender					
Male, n (%)	886 (57)	379 (64)	557 (56)	146 (47)	383 (65)
Female, n (%)	619 (40)	215 (36)	393 (40)	124 (40)	206 (35)
Unknown, n (%)	41 (3)	0 (0)	41 (4)	41 (13)	0 (0)
Age (years)					
n (n missing)	1544 (2)	594 (0)	989 (2)	309 (2)	389 (0)
Mean (SD)	34.8 (25.7)	29 (22.7)	29.4 (24)	16.7 (14.9)	52.7 (18.7)
Median	33.6	18.9	16.8	11	52
Min-Max	0.1-103.1	0.1-80	0.4-97.9	2.3-70.1	5.8-103.1
<4 years, n (%)	82 (5)	55 (9)	30 (3)	11 (4)	0^
4-12 years, n (%)	358 (23)	139 (23)	328 (33)	154 (50)	13 (2)
>12-18 years, n (%)	189 (12)	93 (16)	151 (15)	66 (21)	20 (3)
>18-30 years, n (%)	117 (8)	58 (10)	70 (7)	41 (13)	28 (5)
> 30-50 years, n (%)	326 (21)	115 (19)	188 (19)	12 (4)	206 (35)
>50 - ≤ 64 years, n (%)	250 (16)	79 (13)	131 (13)	23 (7)	172 (29)
≥65 years, n (%)	222 (14)	55 (9)	91 (9)	2 (0.6)	150 (25)
Unknown, n (%)	2 (0)	0	2 (0.2)	2 (0.6)	0
Race					
Caucasian, n (%)	1033 (67)	413 (70)	601 (61)	168 (54)	434 (74)
Black, n (%)	32 (2)	10 (2)	17 (2)	0	23 (4)
Asian, n (%)	104 (7)	68 (11)	4 (0.4)	0	99 (17)
Hispanic, n (%)	3 (<1)	1 (<1)	3 (<1)	0	2 (<1)
Other, n (%)	54 (4)	33 (6)	48 (4.8)	0	31 (5)
Unknown, n (%)	320 (21)	69 (12)	318 (32)	143 (46)	0
Weight (kg)					
n (n missing)	1,527 (19)	592 (2)	974 (17)	311	589 (0)
Mean (SD)	49.5 (22.6)	47.3 (23.5)	45.5 (20.6)	36.5 (17.1)	61.7 (17)
Median	49.6	48	45.5	31.2	61
Min-Max	3.3-175	3.3-116.2	10.0-175	10-105	20-175
< 20 kg, n (%)	144 (9)	79 (13)	92 (9)	45 915)	0*
20-40 kg, n (%)	398 (26)	153 (26)	330 (33)	150 (48)	47 (8)
>40-60 kg, n (%)	500 (32)	194 (33)	309 (31)	85 (27)	244 (41)
>60-80 kg, n (%)	341 (22)	111 (19)	199 (20)	26 (8)	217 (37)
>80 kg, n (%)	144 (9)	55 (9)	44 (3)	5 (2)	81 (14)
Unknown, n (%)	19 (1)	2 (0.3)	17 (2)	0	0

^*Does not include 12 patients from S248.3.003 ages 1-24 months, weight less than 20 kg, who underwent open-label non-treatment run-in.

In studies of CF patients, 351 patients were treated with Creon MMS. Of patients treated with Creon MMS, 78% of were treated for less than four weeks, and 18% of patients were treated for between four and eight weeks. In studies of CF patients, 100% of patients treated with placebo (N=49) were treated with placebo for less than two weeks. These findings are summarized in table 20 below.

Table 20: Duration of Exposure in Cystic Fibrosis Studies

Cystic Fibrosis	Total	Creon MMS	Creon MS	Other PEP	Placebo
Exposure (weeks)					
Any, n (%)	743 (100)	351 (100)	574 (100)	277 (100)	49 (100)
<2 weeks, n (%)	27 (4)	44 (13)	83 (15)	65 (24)	49 (100)
2-4 weeks, n (%)	203 (27)	228 (65)	218 (38)	175 (63)	0
>4-8 weeks, n (%)	307 (41)	64 (18)	180 (31)	16 (6)	0
>8-12 weeks, n (%)	112 (15)	12 (3)	12 (2)	10 (4)	0
>12-26 weeks, n (%)	46 (6)	0	40 (7)	11 (4)	0
>26-52 weeks, n (%)	15 (2)	0	11 (2)	0	0
>52 weeks, n (%)	33 (4)	3 (1)	30 (5)	0	0
Exposure (days)					
n	743	351	574	277	49
Mean (SD)	83 (158)	31 (110)	74 (160)	27 (20)	6 (1)
Median	49	16	28	28	6
Min - Max	2 - 1509	3 - 1509	2 - 883	6 - 134	2 - 9
Sum	61,386	10,893	42,686	7,497	310

In studies of CP patients, 80 patients were treated with Creon MMS, all of whom were treated with Creon MMS for less than four weeks, and 315 patients were treated with placebo at some point during the study. Fifty-four percent (54%) of patients treated with placebo were treated with placebo for less than 2 weeks, and 38% of patients were treated with placebo for between two and four weeks. These findings are summarized in table 21 below.

Table 21: Duration of Exposure in Chronic Pancreatitis Studies

Chronic Pancreatitis	Total	Creon MMS	Creon MS	Other PEP	Placebo
Exposure (weeks)					
Any, n (%)	358 (100)	80 (100)	278 (100)	34 (100)	315 (100)
<2 weeks, n (%)	52 (15)	29 (36)	69 (25)	22 (65)	169 (54)
2-4 weeks, n (%)	61 (17)	51 (64)	161 (58)	12 (35)	120 (38)
>4-8 weeks, n (%)	203 (57)	0	48 (17)	0	26 (8)
>8-12 weeks, n (%)	42 (12)	0	0	0	0
>12-26 weeks, n (%)	0	0	0	0	0
>26-52 weeks, n (%)	0	0	0	0	0
>52 weeks, n (%)	0	0	0	0	0
Exposure (days)					
n	358	80	278	34	315
Mean (SD)	36(19)	12 (3)	24 (13)	14 (5)	16 (10)
Median	33	14	28	11	13
Min - Max	4-84	7-17	1-56	9-22	3-47
Sum	12,869	972	6,554	470	4,873

In studies of post-pancreatic surgery patients, 65 patients were treated with Creon MMS, all of whom were treated with Creon MMS for less than four weeks. Seventy-eight (78) patients were treated with placebo, all of whom were treated with placebo for less than four weeks. These findings are summarized in table 22 below.

Table 22: Duration of Exposure in Post-Pancreatic Surgery Studies

Post-Pancreatic Surgery	Total	Creon MMS	Creon MS	Other PEP	Placebo
Exposure (weeks)					
Any, n (%)	153 (100)	65 (100)	92 (100)	0	78 (100.0)
<2 weeks, n (%)	63 (41)	46 (71)	10 (11)	0	66 (85)
2-4 weeks, n (%)	7 (5)	19 (29)	17 (19)	0	9 (13)
>4-8 weeks, n (%)	69 (45)	0	58 (63)	0	3 (4)
>8-12 weeks, n (%)	14 (9)	0	7 (8)	0	0
>12-26 weeks, n (%)	0	0	0	0	0
>26-52 weeks, n (%)	0	0	0	0	0
>52 weeks, n (%)	0	0	0	0	0
Exposure (days)					
n	153	65	92	-	78
Mean (SD)	30.5 (172)	10.2 (3)	34.8 (14)	-	10.2 (7.7)
Median	29	8	38	-	5
Min - Max	2 - 78	8 - 15	6 - 78	-	2 - 29
Sum	4,662	665	3,200	-	797

For all studies reported in the ISS, the Sponsor provided summary data on lipase exposure in lipase units/kg/day. Because multiple studies did not employ both Creon MMS (CMP) and placebo treatment arms, and multiple studies were designed and executed prior to publication of current dosing guidelines,[1] the ability to draw any safety conclusions based on lipase dosing is limited. Therefore, presentation of lipase dosing in this review is provided for descriptive purposes only. For the 351 patients exposed to Creon MMS in CF trials, exposure ranged from 368 to 17,486 lipase units/kg/day. For the 80 patients exposed to Creon MMS in CP trials, exposure ranged from 811 to 3,727 lipase units/kg/day. For the 65 patients exposed to Creon MMS in post-pancreatic surgery trials, exposure ranged from 845 to 8,016 lipase units/kg/day.

This Reviewer concludes that the Sponsor has assessed the short-term safety of Creon CMP in the appropriate disease populations intended for treatment with Creon, including patients with cystic fibrosis and chronic pancreatitis. Appropriate age groups were also studied, including infants, children, adolescents, and adults. The Sponsor's studies of children with cystic fibrosis as young as one month of age are noteworthy, since recently published guidelines recommend screening all US newborns for cystic fibrosis[7], and initiation of PEP therapy in CF is recommended as soon as CF is diagnosed. Infants with CF are, therefore, a likely treatment population for Creon. Thus, in the opinion of this Reviewer, sufficient clinical information has been provided to support a reasonable assurance of the safety of Creon MMS (CMP) in the likely patient treatment populations.

Successful bridging of the Creon CMP and the TbMP was not established; however. Thus, the safety data obtained with Creon CMP cannot be solely relied upon to establish the safety of Creon TbMP, and at least one short-term safety (and efficacy) clinical trials with the TbMP will be required to support an NDA approval for Creon TbMP.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Given the extensive human exposure to PEPs (and to Creon) since before 1938, the Guidance for submitting NDAs states that animal pharmacology studies with the active ingredient (pancrelipase) are not needed to support the Creon clinical development program. However, toxicology studies are needed if the excipients in the Creon drug product are not classified as Generally Recognized as Safe (GRAS). Consistent with the Guidance, only toxicology studies for the excipient O-phthalic acid (under IND 47,546 and study report S0010.7.637.X) were needed. This information has been extensively reviewed by the Toxicology Reviewer (David Joseph, Ph.D; please see section 3.2 Animal Pharmacology/Toxicology of this review). The conclusion of the Toxicology Reviewer is that animal testing was adequate, and based on results of the submitted four-week oral toxicity study of o-phthalic acid in dogs, the two-year carcinogenicity studies of phthalic anhydride in rats and mice, and other preclinical studies of o-phthalic acid, p-phthalic acid, and phthalic anhydride, the estimated maximum dose of o-phthalic acid resulting from Creon administration is not considered to be a safety concern.

7.2.5 Assessment of Quality and Completeness of Data

Safety information from 57 studies was submitted in the CR of this NDA. Seven studies were not incorporated into the ISS due to data quality issues, including missing data elements, and these studies could not be reviewed for safety. Therefore, the ISS only contains information from the remaining 50 studies. Adequate information was provided to allow substantive individual review of two newly submitted studies: the New Infant CF Study and the New Adult PEI Study.

Appropriate patient populations were studied, including patients with cystic fibrosis from one month of age through adulthood, and adult patients with chronic pancreatitis and pancreatectomy. There was adequate representation of both genders. There was a predominance of Caucasian patients in all studies except the New Adult PEI study wherein predominantly Asian patients were enrolled.

In the opinion of this Reviewer, the quality and completeness of the data allowed for substantive review of Creon MMS (CMP) in patients with PEI due to cystic fibrosis and other causes.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The safety results from the Creon clinical development plan are notable for the following.

Deaths

Eight death reports were included in the ISS and ten death reports were received from other sources (post-marketing and global safety surveillance reports). All deaths were attributable to underlying diseases, including recurrence/metastasis of carcinoma and pre-existing cardiovascular or cardiopulmonary disease. No deaths were attributable to Creon MMS (CMP). No pediatric deaths were reported. This Reviewer concludes that the deaths reported in the Complete Response were attributable to underlying disease and were not causally related to use of Creon MMS (CMP).

SAEs and Withdrawals

- In the ISS, SAEs were reported in 3.4% of patients receiving Creon MMS (CMP) and 3.4% of patients receiving placebo. The most common SAEs by System Organ Class (SOC) were gastrointestinal disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders. The most common SAEs by Preferred Term (PT) were pyrexia, cough, acute bronchitis, superinfection of the lung and hypoglycemia. In the opinion of this Reviewer, there was no clinically meaningful difference in incidence or type of SAEs between Creon MMS (CMP) and placebo treatment groups, and the SAEs reported were generally consistent with underlying disease.

- The most common SAEs in children with cystic fibrosis treated with Creon MMS (CMP) in the three pediatric CF safety studies included in the ISS were gastrointestinal disorders, and upper and lower respiratory tract infections. These SAEs appear to be consistent with underlying disease. An increased incidence of SAEs in children treated with Creon MMS (CMP) in these three studies was noted compared to patients treated with placebo (7% compared to 3%). The relevance of this finding is unclear, but may be explained by a greater exposure time of patients to Creon MMS (about 524 patient-weeks of exposure) than to placebo (about 60 patient-weeks of exposure).

- About 3% of patients in the ISS withdrew, including 2% of patients treated with Creon MMS and 3% in patients treated with placebo. The types of AEs leading to withdrawal were similar to the reported SAEs and commonly reported AEs, and appear to be related to underlying diseases and unrelated to administration of Creon MMS (CMP). An increased incidence of withdrawal was noted in patients with acute pancreatitis, which may be explained by the rapidly changing clinical state in patients with acute pancreatitis.

This Reviewer concludes that SAEs and withdrawals reported in the Safety Update were attributable to underlying disease, were expected in the patient populations under study, and did not appear to be causally related to use of Creon MMS (CMP).

Common Adverse Events

AEs were more common in patients treated with Creon MMS (61%) than in patients treated with placebo (49%). This disparity appears to be due to an increased incidence of less commonly reported AEs in the Creon MMS population, such as epistaxis and nasal congestion, than in patients treated with placebo. This disparity may also be due to differences in study designs for studies included in the ISS (e.g., open-label and lack of placebo control in many studies, which limited the placebo experience). However, the types and frequencies of the most commonly reported AEs in the ISS population are substantially similar between patients treated with Creon MMS (CMP) and patients treated with placebo, and include headaches, abdominal pain and other gastrointestinal complaints, respiratory disorders, and upper and lower respiratory tract infections. There were no obvious differences in the types of AEs reported by patients with different Baseline diagnoses or by age.

Special Safety Considerations with PEPs/Creon

Fibrosing colonopathy has been reported in children with Cystic Fibrosis treated with pancreatic enzyme products. No cases of fibrosing colonopathy (FC) were reported in the ISS, which is not unexpected due to the short duration of the studies and the relatively small safety population. One case of FC was reported in post-marketing reports, which was not definitively attributable to treatment with Creon MMS. Monitoring for FC is to be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products.

Hyperuricemia has been reported in patients with pancreatic exocrine insufficiency treated with PEPs. Though blood and urine uric acid monitoring were was not assessed in all studies in the ISS, hyperuricosuria was noted in several patients in the Prior Pediatric CF and Prior Adult CF Studies, all of whom had non-treatment blood uric acid levels near the upper limit of normal. Monitoring for hyperuricemia is to be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products.

In conclusion, in the opinion of this Reviewer, the safety of Creon MMS (CMP) has been adequately assessed. Withdrawals, SAEs, and non-serious AEs reflect findings reported in the original review of this NDA and in open source literature of patients with cystic fibrosis, and other causes of pancreatic exocrine insufficiency, and commonly include headaches, abdominal pain and other gastrointestinal complaints, respiratory disorders, and upper and lower respiratory tract infections. AEs were most commonly attributable to underlying disease and appear unrelated to administration of Creon MMS (CMP). There were no new or notable safety findings with Creon administration reported in the Safety Update of the CR amendment to the NDA. In addition, all of the appropriate patient populations were studied in the Creon CMP clinical development program, including patients with cystic fibrosis as young as one month of age through adulthood, and patients with PEI due to other causes, such as CP.

Since the Bridging study failed to establish the comparability of the Creon CMP and TbMP, the safety results obtained with Creon CMP cannot be solely relied upon to demonstrate the safety of Creon TbMP, and at least one additional short-term safety (and efficacy) study with Creon TbMP will need to be performed to support the NDA approval of Creon TbMP.

7.3.1 Pooling Data across Studies to Estimate and Compare Incidence

The methodology of the three pediatric cystic fibrosis safety studies allowed for pooling of the safety data for these three studies (see section 7.1.2.3 of this review).

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

In order to optimize therapy while minimizing the risk of fibrosing colonopathy (FC), the Cystic Fibrosis Foundation (CFF), in conjunction with the FDA, recommends starting lipase doses according to age as described below.

The CFF recommends the following dose schedule for full meals:

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.
- Children ≤4 years old eating soft or solid foods: begin with 1,000 USP lipase units/kg/meal.
- Children >4 years old: begin with 500 lipase units/kg/meal.
- Doses in excess of 2,500 USP lipase units/kg/meal should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to significantly improve a documented low coefficient of fat absorption.
- The recommended per meal dose should be halved when ingesting snacks.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with fibrosing colonopathy.

Because safety and efficacy of the Creon TbMP have not been demonstrated in clinical trials, the final dose recommendations may change based on results of clinical trials of the TbMP; however, dosing recommendations for the TbMP should be consistent with current Cystic Fibrosis Foundation guidelines. The Sponsor's proposed dosing in the draft labeling for the CMP for pediatric patients be weight-based, and was generally consistent with the CFF guidelines.

For adult patients with CP and pancreatectomy (PY), dosing should be individualized. (b) (4) This Reviewer recommends that the maximum doses in final labeling not exceed the maximum doses studied for these indications.

8.2 Drug-Drug Interactions

It is expected that patients with PEI may be exposed to prokinetic agents, H-blocking anti-histamines, and antacids. The efficacy studies included in the CR amendment allowed patients to be on these medicines if the dose was stable at the beginning and throughout study. In addition, many patients included in the studies in the CR amendment were on a large number and variety of medications for

treatments of co-morbidities associated with underlying disease (e.g., antibiotics for infectious complications of CF). No reports of drug-drug interactions were noted in the CR amendment. Since Creon is not systemically absorbed, no interactions with systemically-active medications would be expected, although drug-drug interactions were not formally assessed as part of the Creon clinical development program.

8.3 Special Populations

The Creon clinical development program was conducted in patients where PEI is part of primary pathophysiology, including CF, CP, and PY, and in processes where PEI may present less commonly (e.g., diabetes mellitus). The clinical development program focused mainly on patients with CF, CP and PY.

Cystic fibrosis is an autosomal recessive disease estimated to occur in about 1 in 1,500 to 1 in 2,500 live births in the US, and affects an estimated 30,000 persons in the US. No cure exists but supportive treatment with anti-infectives, pancreatic enzyme supplements, and pulmonary, cardiac, and hepatic support has extended life expectancy out of childhood into the fourth and fifth decades. A majority of patients with CF have PEI, and CF patients account for about 42% of the population in the five key studies reviewed (New Infant CF, New Adult PEI, Prior Pediatric CF, Prior Adult CF, and Prior Adult CP Studies). The capacity to respond to treatment, demonstrated by increase in %CFA, appears to mirror severity of PEI, with more severely affected patients demonstrating greater response. This trend in response was seen in infants, youths, and adults with CF.

Studies in patients with cystic fibrosis included patients of both genders. The Sponsor provided information on children from one month of age through adulthood. The Sponsor provided safety information on children with cystic fibrosis less than seven years of age, and provided efficacy data on infants from one through 23 months of age. Adults with cystic fibrosis, from 18 to 53 years were also studied. Though the number of patients studied was small, males and females with CF appear to respond similarly. As expected, from epidemiological characteristics of cystic fibrosis, the CF population studied was predominantly Caucasian; therefore, there is insufficient information to determine any difference in response to treatment in CF patients based on ethnicity.

Pancreatectomy produces definitive and severe PEI. Pancreatectomy is a rare circumstance, offered as a component of treatment for certain gastric or pancreatic cancers, or as a result of trauma care. Patients with PY account for about 29% of the population in the five key studies. Similar to patients with CF, patients with more severe baseline disease demonstrated greater response.

In the opinion of this Reviewer, patients likely to be treated with Creon in the post-marketing setting, including the special populations noted above, have been adequately studied with Creon CMP in the Creon clinical development program.

8.4 Pediatrics

Cystic fibrosis is traditionally diagnosed in childhood, and with the adoption of new screening methods, diagnosis is expected to take place in infancy (e.g., within several weeks of birth). Many children with cystic fibrosis typically display signs and symptoms of malnutrition and pancreatic enzyme deficiency within several months of birth. Because pancreatic enzyme replacements are a mainstay of treatment of patients with pancreatic exocrine insufficiency, it is likely that Creon MMS would be used in infants with CF.

Efficacy was demonstrated in two studies of children from infancy through 17 years of age. In one study of 12 infants from one through 23 months of age, an increase in stool CFA from non-treatment baseline was demonstrated. A second study of 36 children with CF ages 7 through 17 years, also demonstrated benefit (by mean CFA) for the treatment of these patients with Creon. This Reviewer concludes that these efficacy results support the use of Creon MMS (CMP) in children, from one month through 17 years of age.

Two hundred eighty seven (287) children with cystic fibrosis between the ages of one month and 18 years were included in safety analyses. There were 55 children from one month through three years old, 139 children from four through 11 years, and 93 children from 12 through 17 years. It is this Reviewer's opinion that a sufficient number children with cystic fibrosis treated with Creon MMS (CMP) were included to allow analysis of safety in children, including infants as young as one month of age.

This Reviewer concludes that sufficient information was submitted to support the safety and efficacy of Creon MMS (CMP) in children, and children do not appear to respond differently to treatment with Creon than do adults. However, because the Bridging study failed to link the TbMP and CMP, safety and efficacy of the TbMP has not been demonstrated in children.

8.5 Advisory Committee Meeting

No Advisory Committee was convened for this application.

8.6 Literature Review

PEI is well described in the literature as is the use CFA as a measure of efficacy in patients with PEI due to CF [1, 2, 3]. A systematic literature review was not performed.

A list of bibliographic references incorporated into the text of this review is located in Appendix 10.3 of this review.

8.7 Postmarketing Risk Management Plan

No post marketing risk management plan is recommended at this time.

8.8 Other Relevant Materials

There are no other relevant materials being considered.

9 OVERALL ASSESSMENT

9.1 Conclusions

The short-term clinical efficacy and safety of the Creon currently marketed product (CMP) have been demonstrated in children (ages one month through 18 years) and adults with cystic fibrosis (CF), and in adults with pancreatic exocrine insufficiency due to chronic pancreatitis and pancreatectomy. However, a comparison of the Creon CMP and the to-be-marketed product (TbMP) in the Bridging study failed to establish the comparability of the Creon CMP and the TbMP. Therefore, data in this CR amendment are not adequate to support the approval of Creon TbMP. At least one new, short-term clinical efficacy and safety trial with the Creon TbMP will be required for approval of the Creon TbMP, and should be conducted in accordance with the recommendations outlined in the Guidance for submitting PEP NDAs.

9.1.1 Efficacy

Two new short-term clinical efficacy and safety trials of Creon MMS (CMP) in patients with PEI were submitted in this CR amendment to the NDA and were reviewed for efficacy. Three short-term clinical efficacy and safety trials of Creon MMS (CMP) were submitted in the original NDA, and have been previously reviewed and summarized for efficacy during the original NDA review cycle. These five studies collectively enrolled 86 patients with CF, ranging in age from one month to 53 years, and 121 adult patients with PEI due to chronic pancreatitis (CP; n=62), and pancreatectomy (PY, n=59). The primary efficacy measure in these studies was coefficient of stool fat absorption (CFA) from non-treatment or placebo treatment compared with CFA during treatment with Creon MMS (CMP).

Efficacy results from studies are summarized below.

- New Infant CF Study (S248.3.003): In this short term, open-label study of 12 infants with CF, between one and 24 months of age, mean increase in CFA with Creon treatment compared to a no-treatment Baseline was 27% (95% C.I. 12.3, 41.1). Increase in CFA was greatest in four patients with non-treatment CFA less than 40%. Statistical inferences could not be made due to the small size of the study; however the clinical findings showed a clinically meaningful benefit of Creon treatment, and the magnitude of the results are similar to results seen in older pediatric and adult patients with CF. Thus, this study supports the clinical effectiveness of Creon CMP treatment of infants with PEI due to CF as young as one month of age.

- New Adult PEI Study (S245.3.115): In this short term, double-blind, placebo-controlled trial of low-dose and high-dose Creon MMS (CMP) in patients with PEI due to CP (N=35) and PY (N=59), mean increase in CFA for the ITT population (CP and PY) was 12% in patients

receiving high-dose Creon MMS (CMP) compared to placebo (p-value 0.015). In the pancreatectomy sub-population, increase in CFA was approximately 18% in the high-dose Creon group compared to placebo (p-value 0.011). No significant difference in mean CFA compared to placebo was demonstrated in the low-dose Creon group (overall or by sub-population), or in CP patients treated with either low-dose or high-dose Creon CMP.

The Sponsor performed an unplanned interim analysis during the study, and the potential effects on measure of statistical success were not provided. Therefore, no statistical inferences can be made for this study, and this Reviewer concludes that the results of the Adult PEI Study can not be used to support the efficacy of Creon CMP treatment for PEI due to CP or PY.

- Prior Pediatric CF Study (S223.3.101): In this short term, randomized, double-blind, placebo-controlled, treatment withdrawal trial of 38 children with CF, aged 7 through 17 years, CFA was 31% higher (p-value < 0.001) in the Creon MMS (CMP) treatment group (N=18) compared to the placebo group (N=20). These findings show a statistically significant and clinically meaningful benefit of Creon treatment in pediatric patients with PEI due to CF, ages seven years and older.

- Prior Adult CF Study (S223.2.102): In this short term, randomized, double-blind, placebo-controlled, treatment withdrawal trial of 36 adults with CF, ages 18 through 53 years, CFA was 35% higher (p-value < 0.001) in the Creon MMS (CMP) treatment group (N=18) compared to the placebo group (N=18). These findings show a statistically significant and clinically meaningful benefit of Creon treatment in adult patients with PEI due to CF, ages eighteen and older.

- Prior Adult PEI Study (S223.2.01): In this short term, randomized, double-blind, placebo-controlled, treatment trial of 27 adults with CP, ages 38 through 74 years, CFA was 16% higher (p-value 0.0185) in the Creon MMS (CMP) treatment group (N=12) than the placebo group (N=14). These findings show a clinically meaningful benefit of Creon treatment in adult patients with PEI due to CP.

In conclusion, it is the overall assessment of this Reviewer that data from three short-term clinical efficacy and safety studies conducted in pediatric and adult patients with CF, and adult patients with CP support the effectiveness of Creon CMP treatment of steatorrhea in patients with EPI, and that Creon's effectiveness appears to be greatest in the most severely affected patients (i.e., patients with the lowest Baseline CFA). Results from the New Infant CF study were supportive of the clinical effectiveness of Creon CMP in the treatment of steatorrhea in infants with CF, ages one to 24 months these patients, and the results from this study were consistent with the results seen in clinical studies in older pediatric and adult patients. These findings support the labeling of Creon CMP for the treatment of steatorrhea in patients with EPI, ages one month to adult. The results from the New Adult PEI study cannot be used to support the effectiveness of Creon CMP in the treatment of EPI, due to problems with study conduct, and because of the results of the study were not clinically meaningful.

The Sponsor intends to market the Creon TbMP. However, no efficacy and safety clinical trials have been conducted to date with the Creon TbMP. The Bridging study that was submitted to the CR

amendment, and was conducted for the purpose of demonstrating the comparability of the Creon CMP and TbMP products, failed to demonstrate the clinical comparability of the two products. Thus, the efficacy and safety results from studies with the Creon CMP cannot be used to support the clinical efficacy and safety of the Creon TbMP. Therefore, the efficacy (and safety) of the Creon TbMP for the treatment of steatorrhea in patients with EPI has not been demonstrated, and the information submitted in this CR amendment does not support the approval of Creon TbMP.

9.1.2 Safety

The Safety Update in this CR amendment contains information from 57 clinical studies conducted between July 1985 and May 2006, and performed with Creon MMS (CMP) or other formulations that are no longer marketed (e.g., Creon MS). Of the 57 studies in the ISS, 52 are multiple-dose studies and five are single-dose studies. Safety information from 12 of the 57 studies is submitted for the first time in this CR amendment. Seven studies were not incorporated into the ISS due to data quality issues (e.g., inadequate methods for data collection, and incomplete safety datasets), and were not included in this safety review. Therefore, the ISS contains safety information from 50 studies.

The safety results are notable for the following:

Deaths

Eight death reports were included in the ISS and ten death reports were received from other sources (post-marketing and global safety surveillance reports). All deaths were attributable to underlying diseases, including recurrence/metastasis of carcinoma and pre-existing cardiovascular or cardiopulmonary disease. No deaths were attributable to Creon MMS (CMP). No pediatric deaths were reported. This Reviewer concludes that the deaths reported in the Complete Response were attributable to underlying disease and were not causally related to use of Creon MMS (CMP).

SAEs and Withdrawals

- In the ISS, SAEs were reported in 3.4% of patients receiving Creon MMS (CMP) and 3.4% of patients receiving placebo. The most common SAEs by System Organ Class (SOC) were gastrointestinal disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders. The most common SAEs by Preferred Term (PT) were pyrexia, cough, acute bronchitis, superinfection of the lung and hypoglycemia. In the opinion of this Reviewer, there was no clinically meaningful difference in incidence or type of SAEs between Creon MMS (CMP) and placebo treatment groups, and the SAEs reported were generally consistent with underlying disease.

- The most common SAEs in children with cystic fibrosis treated with Creon MMS (CMP) in the three pediatric CF safety studies included in the ISS were gastrointestinal disorders, and upper and lower respiratory tract infections. These SAEs appear to be consistent with underlying disease. An increased incidence of SAEs in children treated with Creon MMS (CMP) in these three studies was noted compared to patients treated with placebo (7% compared to 3%). The relevance of this finding is unclear, but may be explained by a greater exposure time of patients

to Creon MMS (about 524 patient-weeks of exposure) than to placebo (about 60 patient-weeks of exposure).

- About 3% of patients in the ISS withdrew, including 2% of patients treated with Creon MMS and 3% in patients treated with placebo. The types of AEs leading to withdrawal were similar to the reported SAEs and commonly reported AEs, and appear to be related to underlying diseases and unrelated to administration of Creon MMS (CMP). An increased incidence of withdrawal was noted in patients with acute pancreatitis, which may be explained by the rapidly changing clinical state in patients with acute pancreatitis.

This Reviewer concludes that SAEs and withdrawals reported in the Safety Update were attributable to underlying disease, were expected in the patient populations under study, and did not appear to be causally related to use of Creon MMS (CMP).

Common Adverse Events

AEs were more common in patients treated with Creon MMS (61%) than in patients treated with placebo (49%). This disparity appears to be due to an increased incidence of less commonly reported AEs in the Creon MMS population, such as epistaxis and nasal congestion, than in patients treated with placebo. This disparity may also be due to differences in study designs for studies included in the ISS (e.g., open-label and lack of placebo control in many studies, which limited the placebo experience). However, the types and frequencies of the most commonly reported AEs in the ISS population are substantially similar between patients treated with Creon MMS (CMP) and patients treated with placebo, and include headaches, abdominal pain and other gastrointestinal complaints, respiratory disorders, and upper and lower respiratory tract infections. There were no obvious differences in the types of AEs reported by patients with different Baseline diagnoses or by age.

Special Safety Considerations with PEPs/Creon

Fibrosing colonopathy has been reported in children with Cystic Fibrosis treated with pancreatic enzyme products. No cases of fibrosing colonopathy (FC) were reported in the ISS, which is not unexpected due to the short duration of the studies and the relatively small safety population. One case of FC was reported in post-marketing reports, which was not definitively attributable to treatment with Creon MMS. Monitoring for FC is to be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products.

Hyperuricemia has been reported in patients with pancreatic exocrine insufficiency treated with PEPs. Though blood and urine uric acid monitoring were was not assessed in all studies in the ISS, hyperuricosuria was noted in several patients in the Prior Pediatric CF and Prior Adult CF Studies, all of whom had non-treatment blood uric acid levels near the upper limit of normal. Monitoring for hyperuricemia is to be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products.

In conclusion, in the opinion of this Reviewer, the safety of Creon MMS (CMP) has been adequately assessed. Withdrawals, SAEs, and non-serious AEs reflect findings reported in the original review of this NDA and in open source literature of patients with cystic fibrosis, and other causes of pancreatic exocrine insufficiency, and commonly include headaches, abdominal pain and other gastrointestinal complaints, respiratory disorders, and upper and lower respiratory tract infections. AEs were most commonly attributable to underlying disease and appear unrelated to administration of Creon MMS (CMP). There were no new or notable safety findings with Creon administration reported in the Safety Update of the CR amendment to the NDA. In addition, all of the appropriate patient populations were studied in the Creon CMP clinical development program, including patients with cystic fibrosis as young as one month of age through adulthood, and patients with PEI due to other causes, such as CP.

Since the Bridging study failed to establish the comparability of the Creon CMP and TbMP, the safety results obtained with Creon CMP cannot be solely relied upon to demonstrate the safety of Creon TbMP, and at least one additional short-term safety (and efficacy) study with Creon TbMP will need to be performed to support the NDA approval of Creon TbMP.

9.1.3 Conclusion

In conclusion, it is the overall assessment of this Reviewer that data from three clinical short-term efficacy and safety studies conducted in pediatric and adult patients with CF, and in adult patients with CP support the effectiveness of Creon CMP treatment of steatorrhea in patients with PEI. Creon's effectiveness appears to be greatest in the most severely affected patients (i.e., patients with the lowest Baseline CFA). Results from the New Infant CF study were also supportive of the clinical effectiveness of Creon CMP in the treatment of steatorrhea in infants with CF, ages one to 24 months these patients, and the results from this study were consistent with the results seen in clinical studies in older pediatric and adult patients. These findings support the labeling of Creon CMP for the treatment of steatorrhea in patients with PEI, ages one month to adult. The results from the New Adult PEI study can not be used to support the effectiveness of Creon CMP in the treatment of EPI, due to problems with study conduct, and because of the results of the study were not clinically meaningful.

The safety of Creon CMP has also been supported in the short-term clinical efficacy and safety studies, and by the information in the ISS/Safety Update submitted for review in the CR amendment. Overall, no new or notable safety signals were identified in the review of the safety data, the adverse event profile of Creon CMP is felt to be consistent with the profile of Creon (and other PEPs) previously described, and the majority of AEs reported appear to be consistent with underlying disease.

The Sponsor intends to market the TbMP. However, no efficacy and safety clinical trials have been conducted to date with the Creon TbMP. The Bridging study that was submitted to the CR amendment, and was conducted for the purpose of demonstrating the comparability of the Creon CMP and TbMP products, failed to demonstrate the clinical comparability of the two products. Thus, the efficacy and safety results from studies with the Creon CMP cannot be used to support the clinical efficacy and safety of the Creon TbMP. Therefore, the efficacy and safety of the Creon TbMP for the

treatment of steatorrhea in patients with EPI has not been demonstrated, and the information submitted in this CR amendment do not support the approval of Creon TbMP.

9.2 Recommendation on Regulatory Action

This Reviewer recommends an Approvable (AE) action.

The safety and efficacy of the Creon MMS (CMP) have been established for the treatment of steatorrhea in patients with PEI, ages one month to adult. However, except for one bridging study, no clinical trials have been performed with the Creon to-be-marketed product (TbMP). The bridging study failed to establish the clinical comparability of the CMP and TbMP. Therefore, data in this CR are not adequate to support the approval of Creon TbMP.

One or more short term, efficacy and safety clinical trials with Creon TbMP are required to establish the safety and efficacy of the Creon TbMP. These studies are to be performed in patients with pancreatic exocrine insufficiency, such as cystic fibrosis. Efficacy in these clinical trials is to be demonstrated by a change in coefficient of stool fat absorption (CFA) from non-treatment or placebo treatment compared to CFA during treatment with the TbMP.

9.3 Recommendation on Postmarketing Actions

No post-marketing actions are recommended at this time.

9.4 Labeling Review

This Reviewer recommends an approvable action; therefore, review of labeling was not performed.

9.5 Comments to Applicant

Study S245.2003 (e.g., the Bridging study) failed to bridge the currently marketed product (CMP) to the to-be marketed product (TbMP). Therefore, safety and efficacy information of the CMP can not be used to establish safety and efficacy of the TbMP.

One or more a short term, clinical trials of efficacy and safety of Creon MMS (TbMP) are required to establish safety and efficacy of the TbMP. These studies are to be performed in patients with pancreatic exocrine insufficiency, such as cystic fibrosis. Efficacy in these clinical trials is to be demonstrated by a change in coefficient of stool fat absorption (CFA) from non-treatment or placebo treatment compared to CFA during treatment with the TbMP.

Interim analyses may weaken or invalidate statistical inferences of efficacy and should be avoided. If performed, details of planned interim analyses are to be included in your initial study protocol.

Future clinical trials of the TbMP are to be in accordance with the FDA Draft Guidance Document: Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs (located here http://www.fda.gov/Cder/guidance/6275fnl.htm).

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 New Infant CF Study (S248.3.003)

The study was performed with a CMP formulation of MMS, rather than with the TbMP.

10.1.1.1 Study Design

This was an eight-week, open-label, single arm, two-center study of 12 infants, one to 24 months old, that evaluated the efficacy, safety and tolerability of Creon for Children (a brand of Creon MMS) in patients with pancreatic PEI due to CF. On day -10, after screening and informed consent procedures were completed, enrolled patients discontinued prior PEP therapy, if any, at least 72 hours prior to initial dietary fat monitoring and stool collection for Baseline CFA evaluation [day -7 to day -4]. Treatment began on day 1 with a Creon MMS dose of 2,000 lipase units per gram of fat intake. Maximum daily dose was not stated in the protocol. Stool collection for the second CFA (Treatment CFA) was repeated at visit 2 (treatment day 15). Both Baseline and Treatment CFA were both performed during hospitalization for 72-hour fat balance assessment. Safety and secondary efficacy parameters were assessed at visits three (day 36) and four (day 57).

Eligible patients were one to 24 months old with CF, and PEI defined either by age adjusted definitions of steatorrhea or stool chymotrypsin < 5 U/g stool. Patients were required to have Baseline CFA < 70%.

The primary efficacy endpoint was change in CFA (Treatment CFA minus Baseline CFA). Success was defined as Treatment period CFA > 90%. Secondary efficacy measures were effect on steatorrhea and growth parameters including height, weight, and body mass index.

No placebo treatment was administered during Baseline (e.g., wash-out) or Treatment periods. Regardless of prior exposure to any PEP, all patients underwent at least a 72-hour wash-out period prior to the first 72-hour dietary intake assessment and fat balance assessment and subsequent treatment. Patients served as their own controls.

The first patient's first visit was on 27 June 2002, and the final patient's last visit was on 7 September 2004.

10.1.1.2 Study Objectives

Primary objectives were efficacy and safety. The main efficacy parameter was change in CFA Treatment CFA minus Baseline CFA). Successful response was defined as patients with treatment CFA above 90%.

Secondary objectives were evaluation steatorrhea, fecal energy balance, stool characteristics, gastrointestinal symptoms, laboratory parameters; nutritional parameters including weight, height, and weight for height percentile; and patient acceptance.

Note that efficacy will be determined only change in CFA. It is expected that treatment with PEPs positively affects growth parameters in children with CF; however, the study was not of sufficient duration for potential changes in these parameters to be adequately assessed.

10.1.1.3 Eligibility Criteria

Patients were to be between one to 24 months old with a diagnosis CF diagnosed by either two sweat tests or gene analysis, must have had PEI defined by age adjusted steatorrhea (< 4 months, > 4 g/24 hr; 4-12 months, > 3 g/24 hr; > 12 months, > 3-4 g/24 hr) or stool chymotrypsin < 5 U/g stool, and must have had baseline CFA < 70% at end of non-treatment wash-out period.

Patients were excluded if they had severe illness, or other relevant diseases revealed by history, physical, or laboratory assessments which might limit participation in the study. Specific exclusions included clinically evident chest disease, abnormal chest x-ray, meconium ileus or other conditions requiring intestinal resection, allergy to porcine pancreatin, sever allergy or sever abnormal drug reaction, any pancreatic enzyme therapy within three days prior to first hospitalization (Baseline CFA), and any experimental drug within 4 weeks prior to study entry.

10.1.1.4 Concomitant and Prohibited Medications

Any pre-study PEP had to be discontinued at least 72 hours prior to day 1. The following classes of medicines were prohibited except if already in use at a fixed dose at screening: prokinetic agents, antacids, H2 antagonists, proton-pump inhibitors, sucralfate, prostaglandins, CCK-antagonists, biliary acids, and taurine. Any other medicines that were medically required during the study were reported on CRFs.

10.1.1.5 Study Visits and Procedures

Study visits and Procedures are presented in Table 23 below.

Table 23: New Infant CF Study: Flow Chart of Study Visits and					
Phase	**Screening**	**Baseline**	**Treatment**		
	Day -10	Day 1 Visit 1	Day 15 Visit 2	Day 36 Visit 3	Day 57 Visit 4
Hospitalization	Day (-7 to -4)		(Day 12 to 15)		
Demographics	X				
Physical Exam	X				X
Informed Consent	X				
Vital Signs	X	X	X	X	X
Inclusion/Exclusion	X	X			
Chymotrypsin	X		X		
Stool studies[1]	X				
Weight, height, weight for height percentile	X	X	X	X	X
Baseline Complaints		X			
Concomitant Medications		X	X	X	
Lab Assessments[2]	X				
Gastrointestinal symptoms		X	X	X	X
Patient's acceptance			X	X	X
AE collection			X	X	x
Dispense Drug		X	X	X	
Drug collection/compliance review			X	X	X
Diary review		X	X	X	X

[1] CFA, steatorrhea, stool weight, stool consistency, fecal energy loss
[2] Hemoglobin, hematocrit, RBC and WBC count, cholesterol, total protein, serum albumin, blood iron, vitamins A and E

10.1.1.6 Randomization, Blinding and Controls

There was no randomization or blinding. This was an open-label, uncontrolled study.

10.1.1.7 Study Medication Dose Selection, Dispensing, and Compliance

All patients received the same drug dose based on grams of fat intake per-meal.

Creon for Children (batch number 15601) was supplied in glass bottles containing a maximum of 20 g Creon for Children MMS (CMP). The MMS were 0.7 to 1.0 mm. The bottles were packaged with a metered dose spoon. The Sponsor states one dose measure (100 mg MMS) contained 60.36 mg pancreatin with the following enzyme values:

Lipase 5,000 Ph Eur Units
Amylase 3.600 Ph Eur Units
Protease 200 Ph Eur Units

10.1.1.8 Efficacy and Endpoint Measures

The primary outcome measures were stool CFA and safety. Primary efficacy was defined as Treatment CFA minus Baseline CFA. Safety outcomes included any clinically meaningful changes from screening or Baseline, and AE occuring from the beginning of treatment with Creon MMS.

10.1.1.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint was Treatment CFA minus Baseline CFA. Statistical significance was analyzed using a paired t-test. Efficacy was assessed for the ITT and PP population.

10.1.1.8.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints were change in mean stool fat, change in mean stool weight, and increase in dietary fat.

10.1.1.8.3 Safety Assessments

Safety was assessed by type and incidence of AEs; discontinuations due to AEs; drug related AEs, SAEs, and severe AEs; changes from screening visit or Baseline visit in physical exam. vital signs, or clinical laboratory assessments.

10.1.1.8.4 PK and PD Measures

PEPs act locally in the gastrointestinal tract and are not systemically absorbed. Therefore, PK and PD measures were not performed as part of this study.

10.1.1.9 Additional Statistical Considerations

Changes in % CFA are presented as continuous variables, and were summarized by minimum, median, and maximum reported % CFA value, arithmetic mean, standard deviation, and the number of CFA observations. Secondary outcomes (e.g., number of stools per day) were categorical variables and results were summarized absolute and relative frequencies.

10.1.1.10 Protocol Amendment

Due to slow accrual of patients, a single protocol amendment increased the number of study centers from one to two.

10.1.1.11 Study Conduct

The sponsor states the study was performed under ICH/GCP Guidelines. No financial interests were reported.

10.1.1.12 Study Results

10.1.1.12.1 Patient Population and Demographics

Twelve patients were screened, enrolled, and completed the study. The population was comprised of five male and seven female children between the ages of one and 23 months. All patients were Caucasian.

The first dose was administered 06-July-2002, and the final dose was administered 04-September-2004.

10.1.1.12.2 Concomitant Medication

Patients were exposed to 29 non-study medications, including two non- protocol PEPs, administration of which ceased six or greater days prior to the protocol drug treatment dose.

The most common concomitant medications were tocopherol acetate (N=9), multivitamin preparations (N=9), and antibiotics (N=9; Augmentin=1, Ciprofloxacin=2, Colistin=1, Tobral=1, Zimox=1, and Zithromax=3) for treatment of mild to moderate inter-current infections and prophylaxis. Table 27 below lists all concurrent medications. Table 24 below lists concomitant study medications during Creon MMS (CMP) treatment.

Table 24: New Infant CF Study: Most Common Concomitant Medications

Concomitant Medications During Treatment	N (%)
Any concomitant Medication	12 (100)
Other, Plain Vitamin Preparations	12 (100)
Protovit (multivitamin)	9 (75)
Macrolides (Azithromycin)	4 (33)
Paracetamol	3 (25)
Phytomenadione	3 (25)
Prednisone (systemic)	3 (25)

10.1.1.12.3 Compliance with Study Medication

The sponsor states that "poor documentation of compliance" precluded analysis. A record of dispensed and returned medication and weight of unused drug is reported.

Mean exposure time was 59 days (57-64 days).

Mean lipase dose in lipase units/gram/day of fat intake was 2,326 (SD 1,274). Median dose was 1,910 lipase units/gram fat intake/day, and dose range was from 1,159 to 5,148 lipase units/gram fat intake/day.

Mean daily lipase dose was 7,967 u/kg/day (SD 2,071). Table 25 below displays each patients average estimate of average daily dose based on each patient's mean weight over the study period and each patients mean daily dose. Each line represents one patient. All patients are presented.

Table 25: New Infant CF Study Estimated Mean Daily Dose, ITT

	Average Measured Daily Doses	Activity Lipase Units/day	Average Daily Weight (kg)	Mean Daily Dose IU/kg/day
	15.4	77,000	10.6	7,264
	7.5	37,500	5	7,500
	15.5	77,500	11.3	6,858
	25.5	127,500	12.4	10,282
	5.6	28,000	4.1	6,829
	10.3	51,500	6.6	7,803
	11.9	59,500	7.7	7,727
	12.7	63,500	8.5	7,471
	8.4	42,000	8.7	4,827
	30.6	15,3000	11.7	13,077
	9.4	47,000	6.8	6,912
	12.5	62,500	6.9	9,058
Mean	**13.7**	**68,875**	**8.4**	**7,967**
SD	**7.4**	**36,890**	**2.7**	**2,071**

10.1.1.12.4 Protocol Deviations and Violations

Datasets were reviewed and compared with listed protocol deviations and violations. Two patients had major protocol violations (Baseline CFA over 70%). All patients had minor protocol deviations. All patients completed all treatment procedures. All protocol deviations are listed in Table 26 below, copied from Submission vol. 60 p 21,945

Table 26: New Infant CF Study: Protocol Deviations

Category of Deviation	N=12	% Affected
Number of Patients with at Least One Deviation	10	(83.3%)
ASSESSMENT SCHEDULE	8	(66.7%)
Diary entries completely missing on one or more of the planned days	4	(33.3%)
Diary entries incomplete but not completely missing on one or more days	3	(25.0%)
Visit 4 not 56 days +/- 5 days after Visit 1	2	(16.7%)
Duration of stool collection other than 3 days	1	(8.3%)
First screening visit more than 10 days before Visit 1	1	(8.3%)
Last day of second hospitalization not one day before Visit 2	1	(8.3%)
Visit 3 not 35 days +/- 3 days after Visit 1	1	(8.3%)
IN-/EXCLUSION CRITERIA	4	(33.3%)
Deviation from inclusion or exclusion criterion as ticked on CRF pages	4	(33.3%)
Age < 1 or > 24 months	2	(16.7%)
Patient's baseline CFA is ≥ 70%	2	(16.7%)

Patients 1-6 and 2-3 had Baseline CFAs of 71.4 and 70.3%, respectively, which qualified as major protocol violations. Both patients were female. No other protocol deviations resulted in alterations in the ITT or PP populations. The sponsor's table below lists all protocol deviations.

This reviewer determined the two patients with Baseline CFA over 70% should be retained in primary efficacy analysis calculations because their Baseline CFA results were virtually identical to the 70% cut-off given published performance characteristics of the method of CFA analysis.[8]

This reviewer concludes the protocol deviations do not preclude analysis and interpretation of any patient's results.

10.1.1.12.5 Efficacy Analyses

10.1.1.12.5.1 Primary Efficacy Analyses

Primary efficacy is defined as change in CFA (Treatment CFA minus Baseline CFA) in the ITT population. Stool for Baseline CFA was collected starting at ≥ 72 hour non-treatment/wash-out. Stool collection for Treatment CFA began at the two week treatment visit (15th day or Creon MMS treatment).

Mean Baseline CFA for the ITT was 58% (SD=18), mean Treatment CFA was 85% (SD=12), and change in mean CFA was 27% (SD=22, 95% C.I. = 12.9, 40.4). The results are clinically meaningful; however, the Statistician's review indicates the study was not of adequate size to draw statistical inferences. Percentages are rounded to nearest whole number integer.

This reviewer performed an unplanned subgroup analysis which evaluated change in CFA based on Baseline CFA (< 60% and ≥ 60%). In the population with Baseline CFA < 60%, mean Baseline CFA was 41% (SD=25), and mean change in CFA was 43% (SD=27, 95% C.I. = -0.9, 86.1). Individuals with Baseline CFA ≥ 60% had mean Baseline CFA of 66% (SD 4) and mean change in CFA was 19% (SD=14, 95% C.I. = 6.8, 30.6). These results are clinically meaningful but due to the sizes of the study sub-populations no statistical inferences can be made. Percentages in text are rounded to nearest whole number integer. These findings are presented in Tables 27 and 28, and Figure 5 below.

Table 27: New Infant CF Study; Change in CFA (%) by Baseline CFA (%) Category for ITT Population

	All Patients	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: Statistical Reviewer's analysis

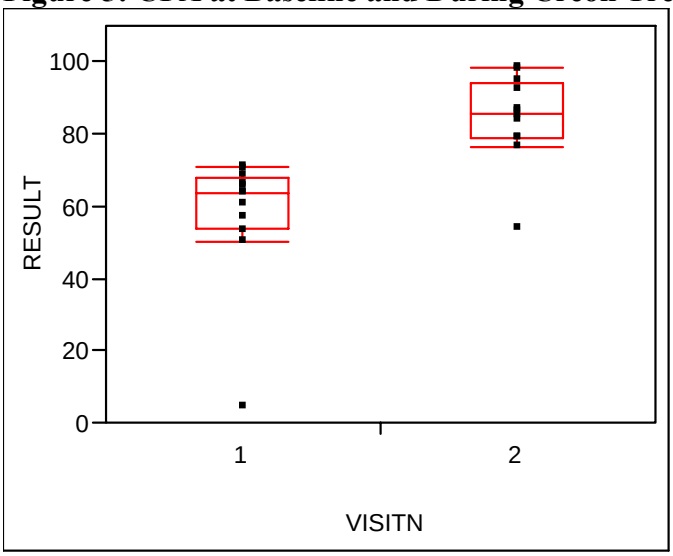
Table 28: New Infant CF Study: Individual Patient Change in CFA Treatment CFA minus Baseline CFA (Mean, SD); ITT

ITT population (N=12)			
	Baseline CFA	Treatment CFA	Change in CFA
	4.7	85.1	80.4
	50.3	95.0	44.7
	53.3	76.5	23.2
	57.1	79.0	21.9
	60.5	98.6	38.1
	63.7	54.3	-9.4
	63.8	87.1	23.3
	65.8	84.1	18.3
	66.5	86.7	20.2
	68.9	98.3	29.4
	70.3	79.1	8.8
	71.4	92.5	21.1
Mean	**58.0**	**84.7**	**26.7**
SD	**18**	**12.1**	**21.7**
CFA (Mean, SD); Baseline CFA < 60% (N=4)			
	4.7	85.1	80.4
	50.3	95	44.7
	53.3	76.5	23.2
	57.1	79	21.9
Mean	**41.4**	**83.9**	**42.6**
SD	**24.6**	**8.2**	**27.3**
CFA (Mean, SD); Baseline CFA ≥ 60% (N=8)			
	60.5	98.6	38.1
	63.7	54.3	-9.4
	63.8	87.1	23.3
	65.8	84.1	18.3
	66.5	86.7	20.2
	68.9	98.3	29.4
	70.3	79.1	8.8
	71.4	92.5	21.1
Mean	**66.4**	**85.1**	**18.7**
SD	**3.7**	**14.2**	**14.2**

[1] Each patient is represented on each line.

The results for CFA at Baseline (no-treatment) and for CFA during Creon treatment for the ITT population are presented graphically in the following figure, Figure 5. The VISITN 1 column represents Baseline encounters and the VISITN 2 column represents encounters during Creon treatment. Each data point along the Y (RESULT) axis represents an individual patient's CFA reported in percent units. The bottom of each closed box delimits the lowest 25th percentile of CFA and the top of each box delimits the upper 75th percentile of CFA. The bottom line under each box delimits the lower 5th percentile of CFA and the topmost line above each box delimits the upper 95th percentile of CFA. The horizontal line within each box represents the median CFA for each treatment period. The dots below the boxes are outliers.

Figure 5: CFA at Baseline and During Creon Treatment in the ITT Population



RESULT: Coefficient of Fat Absorption (CFA) in %
VISITN: Baseline visit (1), treatment period visit (2)

As stated above efficacy will be determined by outcomes in the ITT population; however, this reviewer elected to evaluate change in CFA on the per protocol (PP) population to determine if there were clinically demonstrable differences in efficacy between the ITT and PP populations.

Mean Baseline CFA for the PP was 56% (SD=18.8), mean Treatment CFA was 85% (SD=13), and change in mean CFA was 29% (SD=23). Percentages are rounded to nearest whole number integer. These results are presented in Table 29 and Figure 6 below. Similar to CFA findings in the ITT population results are clinically meaningful, but no statistical inferences may be made.

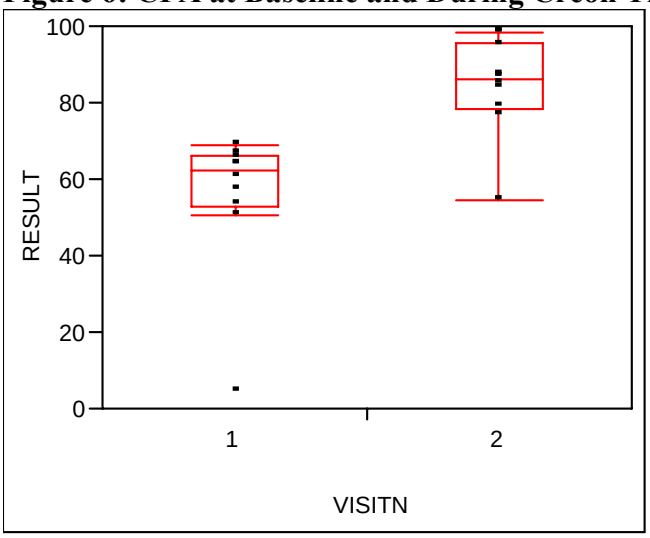
Table 29: New Infant CF Study: Individual Patient Change in CFA Treatment CFA minus Baseline CFA (Mean, SD); PP

PP population (N=10)			
	Baseline CFA	Treatment CFA	Change in CFA
	4.7	85.1	80.4
	50.3	95	44.7
	53.3	76.5	23.2
	57.1	79	21.9
	60.5	98.6	38.1
	63.7	54.3	-9.4
	63.8	87.1	23.3
	65.8	84.1	18.3
	66.5	86.7	20.2
	68.9	98.3	29.4
Mean	**55.5**	**84.5**	**29** [2]
SD	**18.8**	**13**	**23** [2]

[1] Each patient is represented on each line.

The results for CFA at Baseline (no-treatment) and for CFA during Creon treatment for the PP population are presented graphically in the following figure, Figure 6. The VISITN 1 column represents Baseline encounters and the VISITN 2 column represents encounters during Creon treatment. Each data point along the Y (RESULT) axis represents an individual patient's CFA reported in percent units. The bottom of each closed red boxes delimits the lowest 25th percentile of CFA and the top of each red box delimits the upper 75th percentile of CFA. The bottom red line under each box delimits the lower 5th percentile of CFA and the topmost red line above each box delimits the upper 95th percentile of CFA. The horizontal line within each box represents the median CFA for each treatment period.

Figure 6: CFA at Baseline and During Creon Treatment; PP Population



RESULT: Coefficient of Fat Absorption (CFA) in %
VISITN: Baseline visit (1), treatment period visit (2)

10.1.1.12.5.2 Secondary Efficacy Analysis

Secondary efficacy parameters were assessed by comparing changes in number of stools per day, body mass index (BMI), weight and height. Secondary efficacy analyses were not performed on the PP population.

No clinically or statistically meaningful changes were found in BMI or weight-for-height were demonstrated. Baseline measurements of BMI and Weight for Height indicate patients were not nutritionally deficient at time of enrollment which decreased the likelihood of detecting an effect on these two parameters. There was a slight decrease in number of stools per day which was not statistically significant. These findings are summarized in table 30 below. Individual patient results (+/- SD) are presented in Tables 31 (BMI), 32 (weight for height), and 33 (number of stools per day).

Table 30: New Infant CF Study 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: Statistical Reviewer's Analysis, from Table 13 page 48 and Table 16 on page 50 of the Sponsor's study report.
BMI= body Mass Index

Table 31: New Infant CF Study: Change in BMI; ITT (N=12)

BMI	Baseline	Visit 4 (week 8)	Change in BMI kg/m2
	15.3	16.2	0.9
	14.4	17.2	2.8
	16	16.8	0.9
	18.8	17.9	-0.9
	12.7	15.2	2.5
	14	15.8	1.8
	16.1	16.7	0.6
	14	14.3	0.3
	17.1	16.2	-0.9
	16.7	16.1	-0.6
	14.6	15.7	1.1
	17.1	17.4	0.3
Mean	**15.6**	**16.3**	**0.7**
SD	**1.7**	**1**	**1.2**

Table 32: New Infant CF Study: Change in Weight for Height; ITT (N=12)

Weight for Height	Baseline	Visit 4 (week 8)	Change Weight for Height
	99	111	12
	106	107	1
	97	105	8
	114	108	-6
	92	97	5
	86	95	9
	98	99	1
	81	86	5
	99	99	0
	95	95	0
	80	82	2
	115	102	-13
Mean	**96.8**	**98.8**	**2**
SD	**11.3**	**8.7**	**6.8**

There was a slight decrease in number of stools per day which was not statistically significant.

Table 33: New Infant CF Study: Change in Stools/Day; ITT (N=12)

Stools/day	Baseline	Week 8	Change in stool frequency
	4	4	0
	4	2	2
	3	3	0
	2	2	0
	3	0	3
	4	3	1
	4	3	1
	2	3	-1
	1	2	-1
	2	1	1
	2	2	0
	3	1	2
Mean	**2.8**	**2.1**	**0.7**
SD	**1**	**1.1**	**1.2**

Brief comment is made on several characteristics that were neither primary nor secondary efficacy measures. The sponsor reports all patients had steatorrhea on entry, seven patients had steatorrhea at visit four, mean stool weight decreased from 109 to 79 g/day, and mean dietary fat increased from 32 to 34.3 g/day. However, there was insufficient information in the DIARY, CLINSYMP, STOOL_D, GI_D datasets to permit analysis of mean stool weight or changes in dietary fat consumption.

The CLINSYMP dataset shows that two patients had moderate gastrointestinal symptoms (patient 2-1 at visit 1, and Patient 2-3 at visit 2) during treatment. All other entries for gastrointestinal symptoms are recorded as "none". In contradistinction the DIARY dataset indicates patients 1-9 and 2-3 had multiple episodes of "severe" and "none" gastrointestinal symptoms on multiple days. This incongruity was not resolved.

Conflicting data from datasets DIARY and CLINSYMP preclude comment on effect on gastrointestinal symptoms. The DIARY information was recorded by parent or caregiver. The CLINSYMP was recorded at scheduled visits by study investigators or designee.

Laboratory assessments are addressed under the Safety section of this review, 10.1.1.12.3.

10.1.1.12.6 Efficacy Summary

The primary endpoint was Treatment CFA minus Baseline CFA. The ITT population achieved A clinically meaningful increase in CFA was demonstrated in the ITT population (27%, SD=22; 95% C.I 12.9, 40.4). Due to the small size of the study, statistical inferences regarding significant could not be made. Likewise a clinically meaningful increase in CFA was demonstrated in the PP population (29%, SD=23) which also did not reach clinical significance.

Increase in mean CFA of the current study does not reach 30%. However, in four patients with Baseline CFA less than 60% mean increase in CFA was 43% (SD 27, 95% C.I. -0.9, 86.1). These findings are not statistically significant. Four of twelve patients in the ITT achieved pre-designated success with treatment period CFA > 90%; but again, no statistical inference can be drawn. There was no clinically meaningful effect on secondary efficacy parameters.

This reviewer concludes the overall results support clinically meaningful improvement in CFA in the population study with the doses provided.

The study was performed with the CMP. Due to lack of supportive data from the bridging study, primary efficacy trials must be done with the TbMP.

10.1.1.13 Review of Safety

10.1.1.13.1 Reports of Deaths and SAEs

No deaths were reported. No SAEs were reported. No more than six AEs were reported in any patient.

10.1.1.13.2 Treatment Emergent Adverse Events

Three AEs were reported in two patients during the Baseline period. One patient had malnutrition and cow's milk intolerance, and one patient had meteorism. There were 21 non-serious AEs reported during treatment with Creon MMS. The most common AEs by decreasing incidence in the population were pyrexia (33%), cough (25%), constipation (17%), and respiratory tract infections (17%). Conjunctivitis, abdominal pain NOS, viral infection NOS, nasopharyngitis, gastroenteritis adenovirus, rhinitis NOS, and pharyngeal pain each occurred in 8% of the study population. These findings are summarized in table 34 below.

Table 34: All Treatment Emergent AEs in the ITT; New Infant CF Study

		AEs	Patients Reporting AE	% Affected (N=12)
SOC	Preferred Term	Total N=21	N	
Eye Disorders	Conjunctivitis	1	1	8
Gastrointestinal Disorders	Constipation	3	2	17
	Abdominal Pain NOS	1	1	8
General Disorders and Administration Site Conditions	Pyrexia	4	4	33
Infections and Infestations	Viral Infection NOS	1	1	8
	Respiratory Tract Infection NOS	2	2	17
	Nasopharyngitis	3	1	8
	Gastroenteritis Adenovirus	1	1	8
Respiratory, Thoracic and Mediastinal Disorders	Rhinitis NOS	1	1	8
	Pharyngolaryngeal Pain	1	1	8
	Cough	3	3	25

These findings are similar to common complaints in healthy infants and infants with CF. The increased incidence of AEs during double blind treatment compared to the Baseline phase is likely due to the short Baseline period (seven to ten days) compared to the treatment period (eight weeks).

10.1.1.13.3 Vital signs

Vital sign data sets were reviewed and analyzed. Except for fevers recorded as AEs, there were no notable abnormal findings within in the treatment period compared to baseline.

10.1.1.13.4 Laboratory Analyses

Analyses of hematological and biochemical datasets for the ITT population were performed. Due to the small size of the study and the magnitude of change in laboratory parameters, results are presented descriptively (data not shown). Results are not statistically significant.

As expected, decreased concentrations of vitamins A and E were noted at Baseline. There was a slight increase in mean values of vitamins A and E during the study, but mean values remained either below normal or at the lower range of normal for these two analytes. However, clinically meaningful decreases in vitamin E levels were seen in two patients. Marked improvement in vitamins A and E would not be expected due to the short duration of the study.

Also, mean serum cholesterol increased by 0.27 millimol/L, which may be expected with increased lipid absorption with treatment and attendant increase in cholesterol biosynthesis.

10.1.1.14 Safety Summary

The most common AEs by MedDRA Preferred Term were pyrexia (33% affected), cough (25% affected), and constipation and respiratory tract infection (17% affected each). These AEs are similar to the AE profile of the ISS. These findings are similar to and not readily distinguishable from findings in the placebo group of the ISS.

No consistent clinically meaningful laboratory changes are noted.

10.1.1.15 Overall Summary of the New Infant CF Study (S248.3.003)

The study results support efficacy and short term safety in the population studied with the doses used in the trial.

10.1.2 New Adult PEI Study (S245.3.115)

The study was performed with a CMP formulation of MMS, rather than with the TbMP.

10.1.2.1 Study Design

This was a 12 to 13 day, randomized, double blind, parallel group, multi-center study to determine efficacy and safety of Creon MMS in adult patients with PEI due to CP and PY. After successful completion of screening, all patients received 5 days of placebo under single blind conditions, to establish a non-treatment run-in period. On completion of the single blinded placebo phase patients were randomized to receive seven days of treatment with either placebo, 1.5 gram/day (60,000 lipase U/day), or 3.0 gram/day (120,000 lipase U/day) of study drug for eight days under double-blind conditions. Stool collection for CFA was performed after at least 72 hours of single blind treatment (Baseline CFA) and after at least 72 hours of double-blinded treatment (drug or placebo; Treatment CFA). Patients were to maintain a diet containing at least 40 gram/day of dietary fat from immediately prior to study entry through the completion of double blinded treatment; however, this reviewer was unable to determine if patients were provided a standardized diet.

Primary efficacy was defined as the difference in mean Treatment CFA minus Baseline CFA between the low dose group and the placebo treated group, and between the high dose group and the placebo treated group.

Patients were to be at least 20 years old and had to have at least 7.5 g/day of stool fat at screening. The study was performed between 05-June-2000 and 23-June-2003. The ITT population consisted of ninety-four patients.

10.1.2.2 Study Objectives

Primary objectives were to determine efficacy and safety. The primary efficacy parameter the difference in mean Treatment CFA minus Baseline CFA between the low dose group and the placebo treated group and between the high dose group and the placebo treated group.

Secondary objectives were to determine if there were differences in mean Treatment CFA minus Baseline CFA between the low dose group and high dose group.

10.1.2.3 Eligibility Criteria

Patients were eligible for study participation if they were at least 20 years old, and had a diagnosis of either CP or PY with at least 7.5 g/day of stool fat at screening. Prior treatment with PEPs was allowed, but treatment must have ended no later than immediately prior to the beginning of the five-day placebo run-in phase.

Patients were excluded from study participation if their pre-study diet did not consist of at least 40 gram/day of dietary fat; if there was known clinically significant cardiovascular, gastrointestinal (other than primary disease), urogenital, or psychiatric/neurological disease; known allergy to the study drug or similar drug products; acute pancreatitis; superimposed acute pancreatitis, or if pregnant or lactating.

10.1.2.4 Concomitant and Prohibited Medications

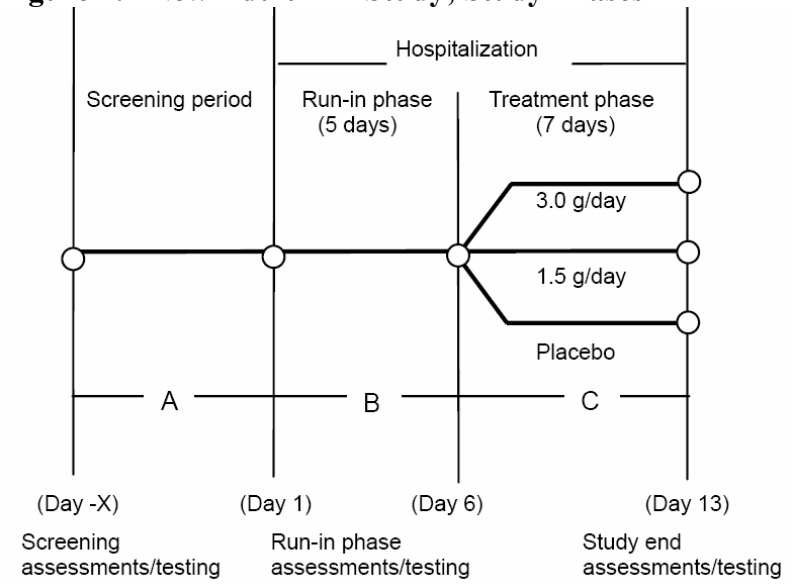
Medicines for pre-existing diseases (e.g., insulin for diabetes mellitus) were allowed. The following medicines were not allowed unless in already in use with a fixed dose at the time of screening: drugs affecting gastric or duodenal pH such as H2-antagonists, antacids and proton pump inhibitors; enhancers of gastric emptying such as erythromycin; antispasmodics, and antitrypsins. The preceding medicines could not be started after the study began.

Prohibited medicines included other digestive enzyme preparations, castor oil, oil cathartics, or oily suppositories during stool collection, and other investigational products.

10.1.2.5 Study Visits and Procedures

The study design and planned procedures are presented in Figure 7 and Table 35 below.

Figure 7: New Adult PEI Study; Study Phases



A: the screening period after obtaining informed consent until the study start
B: the 5-day placebo administration phase
C: the 7-day treatment phase with SA-001 3.0 g/day, 1.5 g/day, or placebo

Table 35: New Adult PEI Study Visits and Procedures

Assessment/testing item	Pre-study	Screening			Run-in phase (hospitalization)						Treatment phase (hospitalization)							
		1	2	3	1		2	3	4	5	6	7	8	9	10	11	12	13
Informed consent explanation	X																	
Informed consent		X																
Demographic and other baseline characteristics		X																
Patient registration (Drug allocation)					X													
Subjective complaint Objective symptom		X				X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration*						R*	R	R	R	R	R/T	T†	T	T	T	T	T	T
Dietary record						X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment compliance							X	X	X	X	X	X	X	X	X	X	X	X
Stool collection				X				<	▬	▬	>				<	▬	▬	>
Body height		X																
Body weight		X																
Blood pressure / Pulse rate		X									X							X
Laboratory tests [1]		X									X							X
Adverse events						X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Clinical laboratory evaluation (hematology, blood chemistry, and urinalysis) and stool fat determination, as well as sample retrieval after stool collection were made by contracted laboratory facilities.
* R: Administration of the study medication for the run-in phase, 3-times daily, except for Day 1 of the run-in phase (twice) and for Day 6 (once)
† T: Administration of the study medication for the treatment phase, 3-times daily, except for Day 6 (twice) and for Day 13 (once)
<▬>: Activity extends from (<), through (▬), to (>).

10.1.2.6 Randomization, Blinding and Controls

A third party study controller made drug-sets consisting of sets of placebo, 1.5 g/day Creon MMS, or 3.0 g/day Creon MMS doses, in random order. Two copies of a medication key-coded randomization table were kept at secure locations and remained unopened. Blinded review and data fixation preceded key-code opening. The study controller retained a code-key in case a medical situation arose necessitating emergent unblinding.

The first study phase was single blinded and the treatment phase was double blinded. The third party study controller corroborated the identity of administered substance (i.e., placebo, 1.5 gram per day dose, or 3.0 gram/day dose) and ensured distribution of correct study substance to correct patient. A designee of the controller assured post-study unidentifiability.

No emergency or pre-mature breakage of the code-key occurred.

10.1.2.7 Study Medication Dose Selection, Dispensing, and Compliance

10.1.2.7.1 Dose Selection

The doses that were studied were selected based on results of a unrelated phase II study of the same product in a similar study population, wherein fixed dosages at 3.0 or 6.0 grams/day, and titrated dosages (0.75, 1.5, and 3.0 gram/day) were administered. The Sponsor states that there was no significant improvement in CFA noted with 0.75 gram/day, that clinical effect with 1.5, 3.0 and 6.0 gram/day were "similar to each other", and there was "no clinically significant difference" in change in CFA between the 3.0 and 6.0 gram/day groups. The Sponsor's also states there was no relationship between adverse events and dose level. The investigators concluded it would be safe to conduct the current trial with placebo, 1.5 gram/day, and 3.0 ram per day dose groups and that there would be no expected benefit by studying 6.0 gram/day.

The study drug for the current study was designated SA-001 and is the same drug that was studied in the phase II study above (e.g., Creon MMS, CMP). The Sponsor states 1 gram of study drug contains 40,000 FIP lipase units, 32,200 amylase units, and 2,400 protease units

A conversion factor for lipase FIP units to lipase USP units is not provided.

10.1.2.7.2 Dispensing and Compliance

During the five day single-blind phase, all patients received placebo dispensed as 0.5 gram per sachets. During the double-blind treatment phase sachets contained either 0.5 gram of placebo or 0.5 gram of drug. Two sachets were provided for each meal. Patients in the placebo group received two 0.5 gram placebo sachets per meal, persons in the 1.5 gram/day group received one 0.5 gram placebo sachet and one 0.5 gram study drug sachet per meal. Patient in the 3 gram/day group received two 0.5 gram study drug sachets per meal.

Patients were hospitalized during the treatment phase. The investigator or their designee assessed compliance at the end of study, or on premature discontinuation by assessing the percentage of sachets consumed (almost all, >75%; forgot some, 50-74%; did not take at least half, not defined; did not take most, not defined; took sachets in too short a time period).

The Sponsor states compliance was 100%.

10.1.2.8 Efficacy and Endpoint Measures

The primary efficacy measure was Treatment CFA minus Baseline CFA.

The primary efficacy population was the ITT population (N=94). This reviewer also performed an efficacy analysis on the PY (N=59) and CP (N=35) sub-populations.

The sponsor also analyzed primary efficacy in the PP population (N=63).

10.1.2.8.1 Primary Efficacy Endpoints

Primary efficacy endpoint was change in CFA in each Creon treated group (low-dose or high dose) compared to change in CFA in the group that received placebo during the double-blind phase. First CFA must have been done after 72 hours of single-blinded placebo.

Efficacy determination was based solely on changes in CFA.

10.1.2.8.2 Secondary Efficacy Endpoint

Secondary efficacy parameters included changes in stool frequency, stool fat determination, and changes in daily calorie and fat intake.

Secondary efficacy endpoints were not used to establish efficacy.

10.1.2.8.3 Safety Assessments

Safety was assessed by type and incidence of AEs; discontinuations due to AEs; drug related serious, and severe AEs; changes in physical exam including vital signs, and clinical laboratory assessments, including clinical chemistry, hematology and urinalysis evaluations.

10.1.2.8.4 PK and PD Measures

Pancreatic enzyme replacement products act locally in the gastrointestinal tract and are not systemically absorbed. Traditional PK and PD measures were not performed as part of this study.

10.1.2.9 Additional Statistical Considerations

The primary efficacy analysis was constructed to compare efficacy of the 3.0 gram/day dose and the 1.5 gram/day dose compared to placebo, and to elicit any dose-response relationship with 1.5 and 3.0 gram/day doses.

Changes in % CFA are presented as continuous variables, and were summarized by minimum, median, and maximum reported % CFA value, arithmetic mean, standard deviation, and the number of CFA observations. Secondary outcomes (e.g., number of stools per day) were categorical variables and results were summarized absolute and relative frequencies.

10.1.2.10 Protocol Amendments

A list of protocol amendments is found in volume 48, page 17,545.

Two related amendments critical to review are now described. One amendment increased size of each treatment group from 18 to 25 patients. The Sponsor states this was done because a prior amendment allowed for a blinded, un-planned interim analysis suggested mean change in CFA and intra-group SD for the placebo group indicated that the original sample size was underpowered to demonstrate treatment effect. The blinded analysis was performed on the subset of patients who had at that time completed both the single-blind non-treatment phase and the double-blind (treatment or placebo) phase.

The Sponsor reports that the interim analysis suggested that the original sample size was underpowered to detect expected change in CFA between Creon treated groups compared to the placebo which were determined in a similar study, [16.6 (SD 17.4) for the low dose group] and [18.6 (SD 11.0) for the high dose group] with 13 patients per treatment group. Therefore, group size was increased from 18 to 25 patients per treatment arm to ensure a 90% power at a two sided significance level of 5%. The preceding information is detailed in volume 48 (pages 17,542 through 17,546) of the Sponsor's CR.

The Statistical reviewer, Dr. Sonia Castillo, concludes that since the interim analysis was not pre-specified and the potential effects on measures of statistical success were not provided, no statistical inferences can be made.

This reviewer concludes the efficacy findings of the New Adult PEI can not be used to support efficacy of Creon CMP for treatment of PEI due to PY or CP.

Another potentially significant stated that the statistical plan was amended prior to breaking the blind to provide for analyses using ANCOVA and ANOVA methods, and also to provide separate analyses for the pancreatectomy and chronic pancreatitis subgroups.

10.1.2.11 Study Conduct

The investigators state GCP was followed. Financial disclosure information was provided. No financial interests were reported.

10.1.2.12 Study Results

10.1.2.12.1 Patient Population and Demographics

Of 156 screened patients, 62 were excluded based on failed screening, withdrawal of consent, or pancreatic carcinoma. There were 94 patients in the ITT; 30 in the placebo group, 31 in the 1.5 gram/day group, and 33 in the 3.0 gram/day group. Thirty five patients had chronic pancreatitis and 59 had pancreatectomy. Gender distribution was unequal (81% men and 19% women). Patient age range was 26-83 years. Fifty patients had prior exposure to PEPs. Demographic information is provided in Table 36 below.

Table 36: New Adult PEI Study Demographic composition of the ITT

Parameter	Phenotype	Placebo	1.5 g/day	3.0 g/day	Total
		(N=30)	(N=31)	(N=33)	(N=94)
Sex (n [%])	Male	26 (87)	24 (77)	26 (79)	76 (81)
	Female	4 (13)	7 (23)	7 (21)	18 (19)
Age (years)	Mean (SD)	65.4 (10.2)	63.7 (9.2)	61.6 (12.4)	
Age (n [%])	21-30	-	-	1 (3)	1 (1)
	31-50	4 (13)	4 (13)	6 (18)	14 (15)
	51-64	8 (27)	8 (26)	11(33)	27 (29)
	65-	18 (60)	19 (61)	15 (46)	52 (55)
Height (cm)	Mean (SD)	161.2 (7.8)	161.2 (7.5)	161.3 (8.6)	
Height (n [%])	≤140	1 (3)	-	-	1 (1)
	141-150	1 (3)	4 (13)	4 (12)	9 (10)
	151-160	9 (30)	10 (32)	11 (33)	30 (32)
	161-170	18 (60)	16 (52)	14 (42)	48 (51)
	≥171	1 (3)	1 (3)	4 (12)	6 (6)
Weight (kg)	Mean (SD)	49.9 (6.2)	51.8 (10.5)	51.0 (8.2)	
Weight (n [%])	-30	1 (3)	-	1 (3)	2 (2)
	31-40	-	4 (13)	2 (6)	6 (6)
	41-50	14 (47)	11 (36)	13 (39)	38 (40)
	51-60	14 (47)	8 (26)	14 (42)	36 (38)
	61-	1 (3)	8 (26)	3 (9)	12 (13)
Diagnosis	Chronic Pancreatitis	12 (40)	11 (35)	12 (36)	35 (37)
	Pancreatectomy	18 (60)	20 (65)	21 (64)	59 (63)
Previous treatment	No	4 (13)	6 (19)	5 (15)	15 (16)
	Yes	26 (87)	25 (81)	28 (85)	79 (84)

10.1.2.12.2 Concomitant Medications

The Sponsor provides a list of all concomitant medicines administered to all patients. An analysis is not provided.

Medicines are listed by a combination of foreign and domestic trade name, drug class name, and generic name. Therefore, ability to perform substantive review is limited and results are presented descriptively.

The most frequently administered medicine classes were different forms of insulin (63% of patients in the placebo group, 45% in low dose, and 33% in high dose) and H-2 blockers (33% of patients in the placebo group, 29% in low dose, and 42% in the high dose group) most commonly famotidine (24% of all patients; 26 % in placebo group, 26% in the low dose group, and 30% in the high dose group).

Administration of anti-infectives was approximately even across treatment groups. Anti-infectives administered during the study included isoniazide (N=4 patients), rifampin (N=2), topical gentamicin-betamethasone (N=3), sulbactam-cefoperazone (N=2), ofloxacin (N=2), and N=1 each of cefaclor, cefotiam hydrochloride, cefpodoxime proxetil, chloramphenicol efradiomycin combined drug, clarithromycin, ketoconazole, clotrimazole, piperacillin sodium, imipenem-cilastatin, and bifonazole

Other commonly administered medicines administered during the study included anxiolytics (triazolam, N=10 patients; brotizolam, N=6; estazolam N=3; flunitrazepam, N=2 flunitrazepam; etizolam, N=2; and N=1 each of diazepam, quazepam, and nitrazepam); senna-base medicines (N=19), magnesium oxide (N=17), prokinetic agents (meospride, N=11 patients and metoclopramide N=4), ursodeoxycholic acid (N=13), camostat mesilate (N=12), and vitamin B-12 analogues (N=11).

There were no clinically meaningful differences in medications administered between treatment groups.

10.1.2.12.3 Compliance with Study Medications

Compliance was 100% by dose sachets per day. One patient took one dose sachet per each of 6 meals per day, rather than two dose sachets per each of three meals per day.

10.1.2.12.4 Protocol Deviations

Thirty-one patients were excluded from the ITT with a total of 40 reasons listed below

21 patients: insufficient stool fat excretion at end of run-in phase (<7.5 gram/day)
7 patients: incomplete stool collection at the end of the run-in phase (5 with no other exclusions
1 patient: unclear fat intake due to vomiting
1 patient: deviation from drug compliance rule
8 patients: insufficient fat intake, last 4 days of run-in or treatment phases (3 with no other exclusions)
2 patients: administration of prohibited medicines (also excluded for reasons above)

The most common protocol deviations are presented in table 37.

Table 37: New Adult PEI Study: List of Important Protocol Deviations

Deviation	Number of Patients with Deviation
Missing stool collections during run-in or treatment phases*	N=7 (Patients: 4-2, 7-3, 10-1, 16-3, 32-1, 40-2, and 45-3)
Change in dose regimen (see 10.1.2.14 above)*	N=1 (Patient 6-1)
Use of prohibited medications	N=7 (Patients 7-2*, 11-1, 12-1*, 16-1, 16-2, 25-1, 29-1)

Prohibited medications included: other enzyme preparations (1), newly prescribe anti-trypsin agent (1), change in dose of antacid (3), newly prescribed prokinetic agent.
* Excluded from per protocol set due to violations above. Patient 16-1 was excluded from the PPS due to < 7.5 gram/day stool fact excretion at end of run-in period.

This reviewer performed an efficacy analysis on the ITT (N=94). One patient was excluded from the low-dose group because there was no stool CFA during double-blind treatment.

10.1.2.12.5 Efficacy analysis

10.1.2.12.5.1 Primary Efficacy Analyses

The primary efficacy endpoint was change in CFA from the double-blind treatment phase (low dose or high dose Creon MMS (CMP), or placebo) minus CFA during single-blind (Baseline) placebo treatment (Treatment CFA minus Baseline CFA). The following efficacy comparisons were made: high-dose treatment group compared to placebo treated group, and low-dose treatment group compared to placebo treatment group.

Results for the primary efficacy endpoint, change in CFA from non-treatment (single-blind placebo) baseline phase compared to the DB (Creon or placebo treatment) phase for the ITT population, showed that change in mean CFA from baseline to DB treatment was 4% for the placebo group, 11% for the low-dose group, and 16% for the high-dose group. Compared to the placebo group, mean CFA change for the low-dose group was 7% (p-value = 0.144), and mean CFA change in the high-dose group was 12% (p-value = 0.015). The clinical meaning of these results is unclear due to an unplanned interim analysis discussed at the end of this section. This reviewer concludes these findings can not be used to support efficacy.

This reviewer also performed subgroup analyses of the primary endpoint for the PY and CP subgroups. For the CP subpopulation, change in mean CFA from baseline to DB treatment was 5% for the placebo group, 9% for the low-dose group and 7% for the high-dose group. Compared to the placebo group, mean CFA change for the low-dose group was 4% (p-value = 0.540), and mean CFA change in the high-dose group was 2% (p-value = 0.781). The clinical meaning of these results is unclear due to an unplanned interim analysis discussed at the end of this section. This reviewer concludes these findings can not be used to support efficacy.

For the PY subpopulation, change in mean CFA from baseline to DB treatment was 3% for the placebo group, 12% for the low-dose group and 20% for the high dose group. Compared to the placebo group, mean CFA change for the low-dose group was 9% (p-value = 0.180), and mean CFA change in the high-dose group was 18% (p-value = 0.011). The clinical meaning of these results is unclear due to an unplanned interim analysis discussed at the end of this section. This reviewer concludes these findings can not be used to support efficacy.

Most patients with Baseline (non-treatment) CFA less than 40%, and therefore capable of demonstrating greatest response, were in the high dose group of the PY sub-population, possibly accounting for the lack of response demonstrated in the CP sub-population and in the PY sub-population treated with low dose Creon CMP.

As discussed in Section 10.1.2.10 above, no statistical inferences can be made based on p-values due to inadequate description of the not pre-specified interim efficacy analysis.

Results of stool CFA analysis are presented in table 38 below. Individual patient baseline, treatment phase, and mean change in CFA are provided for review in tables 39 (ITT), 40 (CP subgroup), and 41 (PY subgroup) below.

Table 38: New Adult PEI Study: Change in Coefficient of Fat Absorption for All Patients by Diagnosis, ITT Population[1]

	Creon 1.5 g/day [3]	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.) [2]	7.1 (4.8)	11.6 (4.7)	
p-value for Mean Treatment Difference	0.144	0.015[4]	
Chronic Pancreatitis			
n	11	11	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[4]	

[1] Source: Statistical Reviewer's Analysis based on ANOVA model with treatment as factor.
[2] Standard Error
[3] One patient included in the FAS in the 1.5 g/day group did not have treatment period CFA performed/recorded thereby reducing n from 31 to 30 patients.
[4] No statistical inferences can be made based on p-values due to inadequate description of an interim efficacy analysis

Table 39: New Adult PEI: Coefficient of Fat Absorption (Mean, SD), ITT Population[1]

	Placebo			Low Dose			High Dose		
	Baseline	**Treatment**	**Change**	**Baseline**	**Treatment**	**Change**	**Baseline**	**Treatment**	**Change**
	WD	--	--	27.1	68.6	41.5	14.7	88.3	73.6
	3.6	-7.8	-11.4	37.7	74.2	36.5	18.3	87.7	69.4
	13.8	43.5	29.7	40	52.2	12.2	20.5	65.1	44.6
	19.1	63.5	44.4	44.1	10.4	-33.7	20.6	65.5	44.9
	23.1	64.7	41.6	51.2	83.8	32.6	30.6	86.6	56
	35.1	45.9	10.8	52.3	92.9	40.6	40	77.4	37.4
	36.3	40.4	4.1	52.9	X	X	52.3	81.3	29
	37.4	54.2	16.8	53.4	82.2	28.8	55.9	55	-0.9
	41.1	55.6	14.5	54.9	64	9.1	60.5	65	4.5
	43.9	64.6	20.7	54.9	74.1	19.2	62.5	81.5	19
	45.2	37.6	-7.6	54.9	86.5	31.6	68.2	87.2	19
	45.4	44.4	-1	57	75.1	18.1	68.1	90.1	22
	49.8	52	2.2	59.4	85.1	25.7	68.9	78.6	9.7
	50.2	41.7	-8.5	59.7	61.1	1.4	69.1	87.7	18.6
	51.6	45.1	-6.5	60.1	81.1	21	70.9	83.7	12.8
	52.8	60.1	7.3	65	80.5	15.5	71.2	90.5	19.3
	54.3	63.9	9.6	66.8	70.9	4.1	73	60.7	-12.3
	54.5	51.3	-3.2	68	48.6	-19.4	76.3	89.1	12.8
	57.7	43.6	-14.1	68.9	82	13.1	78.1	64.8	-13.3
	60.6	61.9	1.3	69.1	87.1	18	81.9	78.8	-3.1
	61	58.5	-2.5	69.3	91	21.7	82.7	97.5	14.8
	63.7	75.7	12	83	79.4	-3.6	84.2	92.4	8.2
	63.9	73.1	9.2	84.1	86.5	2.4	85.9	76.2	-9.7
	66.8	57.2	-9.6	86.7	88.6	1.9	86.2	85.6	-0.6
	83.8	74.5	-9.3	86.8	90.4	3.6	86.3	94.7	8.4
	83.8	87.9	4.1	87.3	76.3	-11	86.3	92.8	6.5
	85.6	71.1	-14.5	91.6	91.2	-0.4	86.7	93.8	7.1
	88.7	88.8	0.1	96	96.9	0.9	87.9	89.2	1.3
	89.6	70.7	-18.9	96	97.1	1.1	87.9	94.9	7
	89.4	85.3	-4.1	96.9	93.4	-3.5	88.8	96.9	8.1
	92.2	90.8	-1.4	94.7	93.3	-1.4	89.7	93	3.3
Mean	**54.8**	**58.7**	**3.9**	**66.8**	**78.2**	**10.9**	91.2	93.4	2.2
SD	**23.6**	**19.8**	**15.4**	**19.1**	**17.8**	**17.6**	95.6	87.3	-8.3
							Mean	**67.9**	**83.4**	**15.5**
							SD	**23.7**	**11.4**	**21.8**

Baseline: CFA during single blind placebo treatment phase
Treatment: CFA during double-blind treatment phase
Change: CFA Treatment minus CFA Baseline
X: CFA data not located; addressed in Statistician's separate analysis
WD: Patient withdrew consent after randomization but prior to single-blind treatment.

Table 40: New Adult PEI: Coefficient of Fat Absorption (Mean, SD), CP sub-population, ITT

	Placebo				Low Dose				High Dose		
	Baseline	**Treatment**	**Change**		**Baseline**	**Treatment**	**Change**		**Baseline**	**Treatment**	**Change**
	23.1	64.7	41.6		54.9	74.1	19.2		40	77.4	37.4
	37.4	54.2	16.8		59.4	85.1	25.7		55.9	55	-0.9
	41.1	55.6	14.5		59.7	61.1	1.4		68.2	87.2	19
	43.9	64.6	20.7		60.1	81.1	21		76.3	89.1	12.8
	45.2	37.6	-7.6		65	80.5	15.5		78.1	64.8	-13.3
	45.4	44.4	-1		68	48.6	-19.4		86.2	85.6	-0.6
	51.6	45.1	-6.5		68.9	82	13.1		86.3	94.7	8.4
	61	58.5	-2.5		69.1	87.1	18		86.7	93.8	7.1
	66.8	57.2	-9.6		86.7	88.6	1.9		87.9	89.2	1.3
	83.8	87.9	4.1		91.6	91.2	-0.4		87.9	94.9	7
	89.4	85.3	-4.1		84.1	86.5	2.4		89.7	93	3.3
	92.2	90.8	-1.4	**Mean**	**69.8**	**78.7**	**8.9**		91.2	93.4	2.2
Mean	**56.7**	**62.2**	**5.4**	**SD**	**12.3**	**12.9**	**13.1**	**Mean**	**77.9**	**84.8**	**6.9**
SD	**22.1**	**17.5**	**15.2**					**SD**	**15.8**	**12.8**	**12.5**

Baseline: CFA during single blind placebo treatment phase
Treatment: CFA during double-blind treatment phase
Change: CFA Treatment minus CFA Baseline

Table 41: New Adult PEI: Coefficient of Fat Absorption (Mean, SD), PY sub-population, ITT

	Placebo				Low Dose				High Dose		
	Baseline	**Treatment**	**Change**		**Baseline**	**Treatment**	**Baseline**		**Change**	**Treatment**	**Baseline**
	3.6	-7.8	-11.4		27.1	68.6	41.5		14.7	88.3	73.6
	13.8	43.5	29.7		37.7	74.2	36.5		18.3	87.7	69.4
	19.1	63.5	44.4		40	52.2	12.2		20.5	65.1	44.6
	35.1	45.9	10.8		44.1	10.4	-33.7		20.6	65.5	44.9
	36.3	40.4	4.1		51.2	83.8	32.6		30.6	86.6	56
	49.8	52	2.2		52.3	92.9	40.6		52.3	81.3	29
	50.2	41.7	-8.5		52.9	X	X		60.5	65	4.5
	52.8	60.1	7.3		53.4	82.2	28.8		62.5	81.5	19
	54.3	63.9	9.6		54.9	64	9.1		68.1	90.1	22
	54.5	51.3	-3.2		54.9	86.5	31.6		68.9	78.6	9.7
	57.7	43.6	-14.1		57	75.1	18.1		69.1	87.7	18.6
	60.6	61.9	1.3		66.8	70.9	4.1		70.9	83.7	12.8
	63.7	75.7	12		69.3	91	21.7		71.2	90.5	19.3
	63.9	73.1	9.2		83	79.4	-3.6		73	60.7	-12.3
	83.8	74.5	-9.3		87.3	76.3	-11		81.9	78.8	-3.1
	85.6	71.1	-14.5		86.8	90.4	3.6		82.7	97.5	14.8
	88.7	88.8	0.1		94.7	93.3	-1.4		84.2	92.4	8.2
	89.6	70.7	-18.9		96	96.9	0.9		85.9	76.2	-9.7
Mean	49.5	56.3	2.8		96	97.1	1.1		86.3	92.8	6.5
SD	30.1	21.3	15.9		96.9	93.4	-3.5		88.8	96.9	8.1
				Mean	65.2	77.8	12.1		95.6	87.3	-8.3
				SD	22.1	20.4	19.9	Mean	62.2	82.6	20.4
								SD	25.9	10.8	24.6

Baseline: CFA during single blind placebo treatment phase
Treatment: CFA during double-blind treatment phase
Change: CFA Treatment minus CFA Baseline
X: CFA data not located; addressed in Statistician's separate analysis

The Sponsor also performed an efficacy analysis on the PP population which excluded 31 patients discussed in section 10.1.2.12.4 above. There is no statistically significant change in CFA in the PP population, or the PY or CP sub-populations. Results are summarized below.

For the entire PP population, mean change in CFA from Baseline to double-blinded treatment was +8% for the placebo group, +15% for the low dose group, and 20% for the high dose group. Mean CFA change compared to the placebo group in the low-dose group was 6% (p-value = 0.332), and was 12% (p-value = 0.055) for the high dose group.

For the CP sub-population of the PP population mean change in CFA from Baseline to double-blinded treatment was 9% for the placebo group, +10% for the low dose group and 12% for the high dose group. Mean CFA change compared to the placebo group was for the low-dose group was 2% (p-value = 0.843), and was 3% (p-value = 0.710) for the high dose group.

For the PY sub-population of the PP population mean change in CFA from Baseline to double-blinded treatment was +8% for the placebo group, +18% for the low dose group and +24 for the high dose group. Mean CFA change compared to the placebo group for the low dose group was 9 % (p-value = 0.322), and was 15% (p-value = 0.086) for the high dose group. The primary efficacy findings for the PP population are presented in Table 42 below. Individual patient baseline, treatment phase, and mean change in CFA are provided for review in Tables 43 (PP), 44 (CP subgroup), and 45 (PY subgroup) below.

Table 42: New Adult PEI Study: Change in CFA (%) for All Patients and by Diagnosis for Per Protocol Population[1]

	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.) [2]	6.2 (6.4)	12.0	
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	

[1] Source: Statistical Reviewer's Analysis based on ANOVA model with treatment as factor.
[2] Standard Error
[3] No statistical inferences can be made based on p-values due to inadequate description of an interim efficacy analysis

Table 43: New Adult PEI: Coefficient of Fat Absorption (Mean, SD), PP Population[1]

	Placebo			Low Dose			High Dose		
	Baseline	**Treatment**	**Change**	**Baseline**	**Treatment**	**Baseline**	**Change**	**Treatment**	**Baseline**
	3.6	-7.8	-11	27.1	68.6	41.5	14.7	88.3	73.6
	13.8	43.5	29.7	37.7	74.2	36.5	18.3	87.7	69.4
	19.1	63.5	44.4	40	52.2	12.2	20.5	65.1	44.6
	23.1	64.7	41.6	44.1	10.4	-33.7	20.6	65.5	44.9
	36.3	40.4	4.1	51.2	83.8	32.6	30.6	86.6	56
	37.4	54.2	16.8	52.3	92.9	40.6	40	77.4	37.4
	41.1	55.6	14.5	54.9	86.5	31.6	52.3	81.3	29
	43.9	64.6	20.7	54.9	74.1	19.2	55.9	55	-0.9
	45.4	44.4	-1	54.9	64	9.1	60.5	65	4.5
	49.8	52	2.2	57	75.1	18.1	68.1	90.1	22
	50.2	41.7	-8.5	59.4	85.1	25.7	68.2	87.2	19
	51.6	45.1	-6.5	59.7	61.1	1.4	69.1	87.7	18.6
	54.3	63.9	9.6	60.1	81.1	21	70.9	83.7	12.8
	54.5	51.3	-3.2	66.8	70.9	4.1	71.2	90.5	19.3
	60.6	61.9	1.3	68	48.6	-19.4	73	60.7	-12.3
	61	58.5	-2.5	68.9	82	13.1	81.9	78.8	-3.1
	63.7	75.7	12	69.1	87.1	18	82.7	97.5	14.8
	63.9	73.1	9.2	69.3	91	21.7	84.2	92.4	8.2
	66.8	57.2	-9.6	83	79.4	-3.6	85.9	76.2	-9.7
	83.8	87.9	4.1	84.1	86.5	2.4	86.2	85.6	-0.6
Mean	**46.2**	**54.6**	**8.4**	**58.1**	**72.7**	**14.6**	86.3	94.7	8.4
SD	**19.8**	**19.1**	**15.9**	**14.2**	**19.1**	**19.3**	86.3	92.8	6.5
							86.7	93.8	7.1
							Mean	**61.5**	**81.9**	**20.4**
							SD	**25.1**	**12**	**23.8**

Baseline: CFA during single blind placebo treatment phase
Treatment: CFA during double-blind treatment phase
Change: CFA Treatment minus CFA Baseline

Table 44: New Adult PEI: Coefficient of Fat Absorption (Mean, SD), CP sub-population PP

	Placebo				Low Dose				High Dose		
	Baseline	**Treatment**	**Baseline**		**Baseline**	**Treatment**	**Baseline**		**Baseline**	**Treatment**	**Baseline**
	23.1	64.7	41.6		54.9	74.1	19.2		40	77.4	37.4
	37.4	54.2	16.8		59.4	85.1	25.7		55.9	55	-0.9
	41.1	55.6	14.5		59.7	61.1	1.4		68.2	87.2	19
	43.9	64.6	20.7		60.1	81.1	21		86.2	85.6	-0.6
	45.4	44.4	-1		68	48.6	-19.4		86.3	94.7	8.4
	51.6	45.1	-6.5		68.9	82	13.1		86.7	93.8	7.1
	61	58.5	-2.5		69.1	87.1	18	**Mean**	**70.6**	**82.3**	**11.7**
	66.8	57.2	-9.6		84.1	86.5	2.4	**SD**	**19.5**	**14.8**	**14.5**
	83.8	87.9	4.1	**Mean**	**65.5**	**75.7**	**10.2**				
Mean	**50.5**	**59.1**	**8.7**	**SD**	**9.2**	**13.9**	**14.7**				
SD	**17.9**	**13**	**16.3**								

Baseline: CFA during single blind placebo treatment phase
Treatment: CFA during double-blind treatment phase
Change: CFA Treatment minus CFA Baseline

Table 45: New Adult PEI: Coefficient of Fat Absorption (Mean, SD), PY sub-population PP

	Placebo				Low Dose				High Dose		
	Baseline	**Treatment**	**Baseline**		**Baseline**	**Treatment**	**Baseline**		**Baseline**	**Treatment**	**Baseline**
	3.6	-7.8	-11.4		27.1	68.6	41.5		14.7	88.3	73.6
	13.8	43.5	29.7		37.7	74.2	36.5		18.3	87.7	69.4
	19.1	63.5	44.4		40	52.2	12.2		20.5	65.1	44.6
	36.3	40.4	4.1		44.1	10.4	-33.7		20.6	65.5	44.9
	49.8	52	2.2		51.2	83.8	32.6		30.6	86.6	56
	50.2	41.7	-8.5		52.3	92.9	40.6		52.3	81.3	29
	54.3	63.9	9.6		54.9	64	9.1		60.5	65	4.5
	54.5	51.3	-3.2		54.9	86.5	31.6		68.1	90.1	22
	60.6	61.9	1.3		57	75.1	18.1		69.1	87.7	18.6
	63.7	75.7	12		66.8	70.9	4.1		70.9	83.7	12.8
	63.9	73.1	9.2		69.3	91	21.7		71.2	90.5	19.3
Mean	**42.7**	**50.8**	**8.1**		83	79.4	-3.6		73	60.7	-12.3
SD	**21.3**	**22.9**	**16.4**	**Mean**	**53.2**	**70.8**	**17.6**		81.9	78.8	-3.1
				SD	**15.2**	**22.3**	**21.9**		82.7	97.5	14.8
									84.2	92.4	8.2
									85.9	76.2	-9.7
									86.3	92.8	6.5
								Mean	**58.3**	**81.8**	**23.5**
								SD	**26.6**	**11.4**	**26**

Baseline: CFA during single blind placebo treatment phase
Treatment: CFA during double-blind treatment phase
Change: CFA Treatment minus CFA Baseline

10.1.2.12.5.2 Secondary Efficacy Analyses

Efficacy determination was based solely on primary efficacy parameters.

Secondary efficacy parameters were descriptive. Secondary efficacy parameters were assessed for the ITT population and the PY and CP sub-populations. Secondary efficacy parameters were not assessed for the PP population or its sub-populations.

Results of stool frequency are presented in Table 46 below. There was no clinically or statistically meaningful change in stool frequency in the ITT population or either the PY or the CP sub-populations.

Table 46: New Adult PEI Study: Change in Stools per Day for All Patients by Diagnosis, ITT Population[1]

	Creon 1.5 g/day [3]	Creon 3 g/day	Placebo
Overall			
n	30	33	30
Baseline mean	6.0	5.5	7.1
Mean change from baseline	-0.23	-0.33	-0.20
Mean Treatment Difference vs. Placebo (s.e.) [2]	-0.03 (0.59)	-0.13 (0.58)	
p-value for Mean Treatment Difference	0.955	0.819	
Chronic Pancreatitis			
n	11	12	12
Baseline mean	5.8	6.2	6.9
Mean change from baseline	-0.36	0.08	-1.25
Mean Treatment Difference vs. Placebo (s.e.)	0.89 (1.00)	1.33 (0.98)	
p-value for Mean Treatment Difference	0.382	0.182	
Pancreatectomy			
n	19	21	18
Baseline mean	6.1	5.2	7.2
Mean change from baseline	-0.16	-0.57	0.50
Mean Treatment Difference vs. Placebo (s.e.)	-0.66 (0.72)	-1.07 (0.71)	
p-value for Mean Treatment Difference	0.367	0.135	

[1] Source: Statistical Reviewer's Analysis based on ANOVA model with treatment as factor.
[2] Standard Error
[3] One patient included in the FAS in the 1.5 g/day group did not have treatment period CFA performed/recorded thereby reducing n from 31 to 30 patients.

Results of changes in caloric intake are presented in Table 47 below. There was no clinically or statistically meaningful change in stool frequency in the ITT population or either the PY or the CP sub-populations. This reviewer notes that diet was not controlled and that assessment of caloric intake was based on patient/care-giver diary reports.

Table 47: New Adult PEI Study: Change in Caloric Intake (kcal/day) for All Patients by Diagnosis, ITT Population[1]

	Creon 1.5 g/day[3]	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.)[2]	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	

[1] Source: Statistical Reviewer's Analysis based on ANOVA model with treatment as factor.
[2] Standard Error
[3] One patient included in the FAS in the 1.5 g/day group did not have treatment period CFA performed/recorded thereby reducing n from 31 to 30 patients.

10.1.2.12.6 Efficacy Summary

The New Adult PEI study evaluated change in CFA from non-treatment (SB placebo) phase to DB treatment (Creon or placebo) phase in adults with PEI due to CP or PY. Compared to the placebo group, the mean CFA change for the low-dose group was 7% (p-value = 0.144), and mean CFA change for the high dose group was 12% (p-value = 0.015). In the PY sub-population, mean increase in CFA for the high-dose group compared to placebo was 18 (p-value - 0.011). Efficacy was not demonstrated in CP patients treated with either low dose or high dose Creon CMP. Most patients with Baseline (non-treatment) CFA less than 40%, and therefore capable of demonstrating greatest response, were in the high dose group of the PY sub-population, possibly accounting for the lack of response demonstrated in the CP sub-population and in the PY sub-population treated with low dose Creon CMP.

The Sponsor performed a non pre-specified interim analysis which suggested that the original study was underpowered to detect the expected change in CFA between the Creon-treated groups compared to the placebo group. Therefore, group size was increased from 18 to 25 patients per treatment arm to ensure a 90% power at a two-sided significance level of 5%. The Statistical Reviewer, Dr. Sonia Castillo, concludes that since the interim analysis was not pre-specified and the potential effects on

measures of statistical success were not provided, no statistical inferences of the efficacy results can be made.

Thus, it is the assessment of this Reviewer that the clinical findings of the New Adult PEI do not support the efficacy of Creon CMP for treatment adult patients with PEI due to PY or CP

Also, the study was performed with the CMP. Due to lack of supportive data from the bridging study, primary efficacy trials must be done with the TbMP.

10.1.2.13 Review of Safety

10.1.2.13.1 Reports of Deaths and SAEs

No treatment emergent deaths were reported.

Three patients experienced SAEs in the single-blind placebo phase (Baseline) including hypoglycemia (N=2 patients), and edema NOS (N=1). Four patients experienced SAEs during the treatment phase. Three patients in the placebo group experienced one SAE each, including pyrexia; subdural hematoma, and hypoglycemia. One patient in the 3 gram/day group experienced pyrexia. No SAE was judged to be related to study drug. No SAE was associated with patient withdrawal from the study. These findings are summarized in Table 48 below.

Table 48: New Adult PEI Study: Treatment Emergent SAEs

SOC term	Preferred Term	N Events	Placebo	1.5g	3.0g
General disorders and administration site conditions	Pyrexia	2	1	0	1
Metabolism and nutrition disorders	Hypoglycemia NOS	1	1	0	0
Nervous system disorders	Subdural hematoma	1	1	0	0

10.1.2.13.2 Treatment Emergent Adverse Events (TEAE)

Forty five patients experienced between 1 and 13 non-serious AEs during the placebo run-in period. The most common AEs during the placebo run-in period were diarrhea (9% patients), hypoglycemia (7%), and abdominal distension, loose stools, and abnormalities of alanine aminotransferase and aspartic acid aminotransferase (5% each). AEs during the placebo run-in period were less common in the group randomized to receive placebo during double blind treatment (40% of patients in the placebo group, 52% of patients the low dose group, and 52% of patients in the high dose group). Results are summarized in Table 49 below.

Treatment 49: New Adult PEI Study: AEs occuring in ≥ 3% patients during single-blind placebo phase

Total Patients by Treatment		Total (N=94)		1.5 g/day (N=31)		3 g/day (N=33)		Placebo (N=30)	
SOC	Preferred Term	n	%	n	%	n	%	n	%
Gastrointestinal disorders	Diarrhea NOS	8	9	4	13	3	9	1	3
	Abdominal distension	5	5	2	7	3	9	0	0
	Loose stools	5	5	1	3	2	6	2	7
	Abdominal pain NOS	4	4	2	7	1	3	1	3
	Constipation	3	3	3	10	0	0	0	0
General disorders and administration site conditions	Pyrexia	3	3	1	3	1	3	1	3
Investigations	Alanine aminotransferase increased	5	5	1	3	3	9	1	3
	Aspartate aminotransferase increased	5	5	1	3	3	9	1	3
	Blood cholesterol decreased	4	4	0	0	3	9	1	3
	Blood albumin decreased	3	3	0	0	2	6	1	3
	Blood glucose decreased	3	3	0	0	1	3	2	7
	Gamma-glutamyltransferase increased	3	3	2	7	1	3	0	0
	High density lipoprotein decreased	3	3	0	0	2	6	1	3
	Protein total decreased	3	3	0	0	2	6	1	3
	Platelet count decreased	2	2	0	0	2	6	0	0
Metabolism and nutrition disorders	Hypoglycemia NOS	7	7	1	3	3	9	3	10
Musculoskeletal and connective tissue disorders	Arthralgia	3	3	0	0	2	6	1	3

n: number of patients experiencing an event one or more times

There were 158 AEs in 64 patients during double-blind treatment (see Table 50 below). AEs were reported in 63% of patients in the placebo group, 70% of patients in the high-dose group, and 74% of patients in the low-dose group. The most common AEs across all treatment groups were abdominal pain (10%), constipation (9%), and abdominal distension, diarrhea and malaise (7% each). Review of the study report, CRFs, and datasets does not provide any rationale why AEs were less common in the placebo treated group. However, it is noted the group randomized to receive placebo during the double blind period had a similarly lower incidence of AE during the baseline phase.

The most common AEs in the placebo group were malaise (14%), abdominal pain, abdominal distension, and hypoglycemia (10% each). The most common AEs in the low dose group were abdominal pain, back pain, and headache (10% each). The most common AEs in the high dose group were constipation and diarrhea (15% each), followed by abdominal pain, vomiting, and gastrointestinal upset (9% each).

Table 50 lists all treatment emergent AEs occuring in > 3% of patients.

Table 50: New Adult PEI Study, AEs reported ≥ 3 patients, by treatment group

All patients by treatment		Total (N=94)			1.5 g/day (N=31)			3 g/day (N=33)			Placebo (N=30)		
		AEs	N	%	AE	N	%	AE	N	%	AE	N	%
		158	65	69	41	23	74	63	23	70	54	19	63
Listing of Individual AEs													
SOC	Preferred Term	AEs	N	%	AE	N	%	AE	N	%	AE	N	%
Gastrointestinal disorders	Abdominal pain NOS	9	9	10	3	3	10	3	3	9	3	3	10
	Abdominal distension	8	7	7	3	2	7	2	2	6	3	3	10
	Constipation	8	8	9	1	1	3	5	5	15	2	2	7
	Diarrhea NOS	7	7	7	0	0	0	5	5	15	2	2	7
	Loose stools	6	6	6	2	2	7	2	2	6	2	2	7
	Vomiting NOS	4	4	4	1	1	3	3	3	9	0	0	0
	Gastrointestinal upset	3	3	3	0	0	0	3	3	9	0	0	0
General disorders and administration site conditions	Malaise	7	7	7	1	1	3	2	2	6	4	4	13
	Chest discomfort	3	3	3	0	0	0	1	1	3	2	2	7
Investigations	Blood glucose increased	6	6	6	1	1	3	3	3	9	2	2	7
	Glucose urine present	3	3	3	2	2	7	0	0	0	1	1	3
Metabolism and nutrition disorders	Hypoglycemia NOS	4	4	4	0	0	0	1	1	3	3	3	10
Musculoskeletal and connective tissue disorders	Back pain	4	4	4	3	3	10	1	1	3	0	0	0
Nervous system disorders	Headache	4	4	4	3	3	10	1	1	3	0	0	0
	Dizziness	3	3	3	0	0	0	1	1	3	2	2	7
Skin and subcutaneous tissue disorders	Cold sweat	3	3	3	0	0	0	2	2	6	1	1	3
	Pruritus	3	3	3	2	2	7	0	0	0	1	1	3

Adverse events were classified as treatment related if the relationship of the event to treatment) was classified as possible, probable, highly probable, or unknown. Treatment related events were reported in the placebo (N=13), low dose (N=8), and high dose (N=21) groups. In depth review of the datasets and accompanying CRFs found no apparent difference in the occurrence of moderate and severe non-serious AEs (8 events in 3 patients in the placebo group; five events in four patients in the low-dose group; and six events in four patients in the high-dose group). No moderate or severe AE was related to drug administration. (Data not shown)

This reviewer concludes AEs in the placebo and treatment group reflect underlying pathophysiology, and that treatment of Adult patients with PEI due to PY and CP with Creon MMS does not increase risk of AEs. This safety information is adequate to inform labeling of Creon MMS (CMP) in patients with PEI due to PY and CP.

10.1.2.13.3 Laboratory Analyses

The laboratory datasets were reviewed in depth. The most common biochemical abnormality was hyperglycemia. Sixty-one of 94 patients had one or more recorded episodes of hyperglycemia or

hypoglycemia. Ten of 11 patients changes in blood glucose classified as clinically relevant by the Sponsor had hyperglycemia one or more times. All ten of these patients had pre-existing diagnoses of diabetes mellitus.

Ninety-three of 94 patients had one or more abnormal urine parameters on one or more urinalyses. Glucosuria was the most common treatment phase urine abnormality. All patients with more than "+/-" glucosuria had hyperglycemia and pre-enrollment diagnosis of diabetes mellitus. There were no clinically meaningful trends in other urine parameters within or across treatment groups.

No clinically meaningful changes were seen in hematologic parameters (see table 51, below).

Table 51: Hematologic characteristics, Mean (SD) for all treatment groups, ITT

Laboratory Parameter	Phase	Placebo		Low Dose		High Dose	
		Mean	SD	Mean	SD	Mean	SD
WBC	Baseline	6,010	2,115	5,484	1,934	5,968	2,093
	Treatment	5,748	1,816	5,650	1,979	6,450	2,093
	Change	-262	1,323	240	1004	375	2,225
RBC	Baseline	376	62	389	57	400	50
	Treatment	375	55	383	62	396	64
	Change	-1.6	20.3	-0.5	20	1.9	28.6
Hemoglobin	Baseline	11.7	1.9	12.1	1.7	12.5	1.7
	Treatment	11.7	1.7	11.9	1.9	12.4	2.1
	Change	-0.0	0.7	-0.1	0.7	0.1	0.9
Hematocrit	Baseline	35.4	5.3	36.2	4.8	37.6	4.8
	Treatment	35.0	4.9	35.6	5.3	37.2	6.0
	Change	-0.3	1.9	-0.2	1.9	0.175	2.8
Platelet	Baseline	239.9	94.9	218.9	57.8	187.0	59.0
	Treatment	211.1	86.8	202.4	59.4	199.6	61.6
	Change	-18.2	27.0	-8.9	24.1	7.9	24.4

No clinically meaningful changes were seen in lipid parameters, or uric acid. Mean Baseline and Treatment period blood glucose values were above normal for all groups. The results are summarized in table 52, below.

Table 52: New Adult PEI Study: Triglycerides, Total cholesterol, HDL Cholesterol, Blood Glucose, and Uric acid for all treatment groups, ITT

Laboratory Parameter	Phase	Placebo		1.5 gram/day		3.0 gram/day	
		Mean	SD	Mean	SD	Mean	SD
Triglycerides	Baseline	79	35	99	54	84	43
	Treatment	75	33	94	47	90	51
	Change	-4	19	-5	24	6	31
Total Cholesterol	Baseline	137	38	146	40	144	43
	Treatment	133	41	157	43	159	42
	Change	-4	17	10	18	15	22
HDL Cholesterol	Baseline	47	15	45	11	47	18
	Treatment	48	16	49	15	50	20
	Change	0.3	7	4	8	3	7
Glucose	Baseline	115	56	128	51	126	55
	Treatment	154	90	136	58	138	52
	Change	39	64	8	33	12	49
Uric Acid	Baseline	5.2	1.6	5.1	1.5	4.8	1.6
	Treatment	5.0	1.5	4.7	1.6	4.8	1.6
	Change	-0.2	0.5	-0.4	0.7	-0.1	0.7

10.1.2.13.4 Vital Signs

Vital sign data sets were reviewed and analyzed. There were no clinically meaningful trends seen within or between treatment groups compared to baseline. These results are summarized in table 53 below.

Table 53: New Adult PEI Study: Vital Signs (Mean, SD)

Vital sign parameter	Phase	Placebo		Low Dose		High Dose	
		Mean	SD	Mean	SD	Mean	SD
Systolic blood pressure (mmHg)	Baseline	116.2	19.0	114.8	16.1	119.0	17.8
	Treatment	119.4	17.3	115.3	19.3	122.6	18.6
	Change	3.2	14.7	0.5	11.7	3.6	16.6
Diastolic blood pressure (mmHg)	Baseline	69.8	9.7	69.0	9.9	69.0	11.5
	Treatment	71.1	8.5	68.4	9.4	70.5	10.0
	Change	1.3	10.6	-0.6	8.9	1.5	10.2
Pulse rate (bpm)	Baseline	69.1	9.8	72.2	10.9	72.4	13.1
	Treatment	68.9	11.7	71.7	9.1	75.3	11.0
	Change	-0.2	9.0	-0.5	8.8	2.9	10.5

10.1.2.14 Safety Summary

The most common AEs across all treatment groups were abdominal pain (9.6%), constipation (8.5%), and abdominal distension, diarrhea and malaise (7.4% each).

The most common AEs in the placebo group were malaise (13.7%), abdominal pain, abdominal distension, and hypoglycemia (10% each). The most common AEs in the low dose group were

abdominal pain, back pain, and headache (10% each). The most common AEs in the high dose group were constipation and diarrhea (15% each), followed by abdominal pain, vomiting, and gastrointestinal upset (9% each).

There was no meaningful difference in AE profile between treatment groups. There was no meaningful trend in laboratory analyses between groups.

No consistent clinically meaningful laboratory abnormalities are noted. Of note, there was no trend toward increase in uric acid in any of the treatment groups.

There were no meaningful trends in vital signs.

The safety findings in this study closely mirror safety findings in the ISS and safety findings reported in the prior review of this NDA (Fathia Gibril November 2003). The safety findings are similar to, and not readily distinguishable from, findings commonly caused by the underlying disease states.

This study was performed with the CMP.

10.1.2.15 Overall Summary of the New Adult PEI Study (S245.3115)

Efficacy is suggested in the high-dose treatment group of the ITT and the pancreatectomy sub-group of the ITT. However, as described in Section 10.1.2.10 above, since the interim analysis was not pre-specified and the potential effects on measures of statistical success were not provided, no statistical inferences can be made.

This reviewer concludes the efficacy findings of the New Adult PEI can not be used to support efficacy of Creon CMP for treatment of PEI due to PY or CP.

The clinical study was not performed with the CMP and further clinical studies are required with the TbMP.

10.1.3 Descriptions of All Deaths Reported in the Complete Response

10.1.3.1 Deaths Reported in the ISS

Eight deaths were described in the ISS. Seven deaths reported for the first time in this CR. One death was reported in the prior submission of this NDA. These deaths appear attributable to primary disease, known complications of primary disease, and age related secondary pathology (e.g., cardiovascular disease). No deaths appear attributable to treatment with Creon MMS.

Study 223.8.01, patient 111 (Creon MS): The patient was a, 11 ½ year old boy who developed cough, fever, chest pain, respiratory failure and renal failure. This patient had a history of pulmonary complications, methicillin resistant staphylococcus aureus (MRSA), and depression. He entered the study on (b) (6) and was treated with Creon during the run in phase and the treatment phase, commencing on day 9. At an undetermined time during the study, the patient was admitted to the hospital with a four day history of fever, and chest pain, productive cough and shortness of breath. He developed an allergic reaction to an unstated stimulus. He was placed on anti-infective therapy (vancomycin, imipenem, and rifampin) and respiratory therapy (undefined) was initiated. The patient was withdrawn from study on day 20 and parenteral nutrition was initiated, followed by increased oxygen requirement due to respiratory distress. On day 30 the patient died from cardiopulmonary arrest. The events were not felt to be related to the study drug.

The study report for 223.8.01 and the individual case report form for patient 111 are not contained in the NDA update.

Study Creo.630, patient 7 (Creon MS, Creon 12,000): The patient was a 71 year old man with pre-existing history of Parkinsonism and urinary and fecal incontinence who presented with declining appetite and altered general state on study day 58. The patient was hospitalized and diagnosed with a severe dehydration, malnutrition, and a urinary tract infection for which he was started on Bactrim. The patient died on study day 77. The cause of death is not stated. The alteration in mental state was not regarded as related to the study drug. The ISS data set states the cause of AE and subsequent death is not related to study drug. The case report form was reviewed.

Study Creo.630, patient 10 (Creon MS, Creon 12,000): The patient was an 89 year old woman with a history of cardiac insufficiency and atrial fibrillation who died on study day 22 due to acute cardiac decompensation. The AE and death were not related to the study drug. The case report form was reviewed.

Study Creo.630, patient 30 (Creon MS, Creon 12,000): The patient was an 89 year old woman with a previous history of phlebitis and perforated ulcer, who died on study day three due to rupture of a previously undiagnosed aortic aneurysm. The AE and death were not related to the study drug. The case report form was reviewed.

Study Creo.630, patient 5 (Placebo): The patient was an 89 year old woman with a previous history of angina and asthma, who was hospitalized on day 30 due to bronchial infection. She died on day 37 due to cardio-pulmonary decompensation. The AE and death were not related to the study drug. The case report form was reviewed.

Study Creo.630, patient 11 (Placebo): The patient was an 87 year old woman with a previous history of hypertension and "arteriopathy" who died one day after receiving her last placebo dose (day 97). Directly antecedent to death, the patient experienced broncho-pulmonary infection, melena complicated by acute anemia, dehydration, and coma. The AE and death were not felt to be related to administration of placebo. The case report form was reviewed.

Study Creo.631, patient 39 (Placebo): The patient was a 77 year old man with history of carotid and coronary vascular disease who developed cardiovascular failure on treatment day 43 and died on day 44. The AE and death were not felt to be related to administration of placebo. The case report form was reviewed.

Study S245.3.117, patient 1-C-1 (referred to in ISS dataset as patient 1001, Creon MMS): The patient was a 21 year old man with previous history of pulmonary symptoms related to cystic fibrosis. His last dose of study drug was received on day 773, and he was hospitalized for aggravation of cough, which began on day 770. On day 784 he developed respiratory failure. He developed renal failure (day 795) and circulatory failure (day 796). He died on day 802. The Sponsor states the AEs were not treatment emergent and all AEs were unrelated to study drug.

The case report form was reviewed. The day 770 AE, cough, is treatment emergent. A relationship between cough, respiratory failure, and death can not be ruled out. A relationship of the AEs to treatment is unlikely.

10.1.3.2 Deaths Reports Received from Post-Marketing reports or Studies Not Included in the ISS

Ten death reports were received from post-marketing reports or from studies that were not included in the ISS. These deaths appear attributable to primary disease, known complications of primary disease, and age related secondary pathology (e.g., cardiovascular disease). No deaths appear attributable to treatment with Creon MMS.

Study 245.3.103, patient 2102-L-01 (Creon MMS): The patient was a 66 year old woman with a history of pancreatectomy due to carcinoma of the gall bladder. On treatment day 169 hepatic metastasis of gall bladder carcinoma was reported. She discontinued the study due to persistent diarrhea, which the Sponsor attributed to cancer related chemotherapy. Seven months after discontinuation, she died of respiratory failure. The original AE and subsequent death were unrelated to treatment. The case report form was reviewed.

Study S245.3.104, patient 2032-O-04 (Creon MMS): The patient was a 52 year old man with a history of pancreatic carcinoma. He died of liver failure due to metastatic carcinoma. 54 days after completion of the study. Metastasis was diagnosed two days before receipt of first study dose

(placebo in phase 1). The AE and subsequent death were unrelated to treatment. The case report form was reviewed.

Study S245.3.103, patient 2170-L-01 (compassionate use, drug formulation not stated): The patient was a 55 year old male with a history of pancreatic carcinoma who died of recurrent metastatic disease during an open label compassionate use program. The patient was originally enrolled in study S245.3.103 and was treated with Creon in study from December 1996 through April 1999. The patient died in (b) (6). There was no relationship between the AE, subsequent death, and the study medication. No case report form is found for review.

Patient 1030-C-01, (compassionate use, drug formulation not stated): The patient was a 9 year old boy with history of cystic fibrosis who died of respiratory failure during the compassionate use program. Treatment began in November 1996, under Study 245.2.002, and death occurred in (b) (6). No case report form is found for review. The investigator determined the relationship of the AE to treatment and death is temporally related, but casually unrelated. No case report form is found for review.

Patient 2200-C-01 (compassionate use, drug formulation not stated): The patient was a 10 year old girl with cystic fibrosis who died of respiratory failure during the compassionate use program. Treatment began in August 1996, under Study 245.2.002, and was discontinued on 25 October 1998. The patient died on (b) (6). The AE and death occurred were considered unrelated to medication. No case report form is found for review.

Patient 2140-L-02 (compassionate use, drug formulation not stated): The patient was a 70 year old man with a history of chronic pancreatitis, who died of a subdural hemorrhage secondary to a fall, on (b) (6) during the compassionate use program. The patient was originally in Study S245.3.104 and started Creon February 1997 and discontinued treatment on 8 September 1999. The patient died on (b) (6) The AE and death occurred were considered unrelated to medication. No case report form is found for review.

Patient 22 (Protocol Laugier, Creon MS—Burundi): The patient's age is not known. The patient had chronic pancreatitis, cardiomyopathy, and positive HIV serology. During the second month of treatment the patient died; cause unknown. No case report form is found for review.

Patient 21 (Protocol Laugier, Creon MS—Burundi): The patient was 38 years old and had chronic pancreatitis and hypertrophy of the pancreatic head. The patient died of pancreatic cancer during the first month of treatment. No case report form is found for review.

Study S245.4.007, patient 208 (In blinded study not submitted for review; drug formulation not stated): The patient is an 85 year old woman with a history of hypertension and Parkinson's disease, who died of metastatic gastric cancer and pneumonia. She received treatment for suspected pneumonia with penicillin. The AE and subsequent death are not related to treatment. The case report form was reviewed.

Study S245.4.007, patient 403 (In blinded study, study not submitted; drug formulation not stated): The patient was a 75 year old woman who died from recurrent peritoneal carcinosis. The AE and subsequent death are not related to treatment. The case report form was reviewed.

10.1.4 Safety Summary of Three Studies Not Integrated into the ISS

This Reviewer performed brief summary analyses on three of the seven studies which were not integrated into the ISS. This was done to determine if there were notable differences in between the ISS and the non-integrated studies. Because there was sufficient clinical information to make a determination of safety and efficacy based on the bridging study, the two new clinical trials, and the ISS and because the open label nature of these studies limits assessment of causality of AEs, the incidence of common AEs and other safety parameters was not assessed..

The Long Term PEI exposure study was selected because exposure was 48 weeks. The PEI Dose Comparison Study and the 1-Week Adult PEI Study were chosen because patients from these two studies were eligible for enrollment in the Long Term PEI study. Brief descriptions of the studies are presented, followed by presentation of pooled safety data from the three studies.

The Long Term PEI Exposure Study (S245.3.103) was a 48 week, OL, non-PC, dose comparison study of Creon MMS (3 gram/day and 6 gram/day) in 63 patients with PEI due to CP, PY, and other, non-specified, causes of pancreatic insufficiency. The safety population included N=61 patients. The uncontrolled nature of this study precluded substantive review of efficacy; however design allowed for assessment of AEs. On enrollment, patients who were previously enrolled in the PEI Dose Comparison Study and the 1-Week Adult PEI Study, described below, were assigned a unique study-patient identifier. Sixty three patients received Creon MMS, and no patients received placebo.

The PEI Dose Comparison Study (K245.5.703) was three week OL study of Creon MMS in 43 adults with PEI due to CP or PY. All patients received 5-days of OL placebo treatment. After completion of the placebo phase, 41 patients were randomized into one of two active treatment sub-studies. In one sub-study, patients were treated with either of two fixed doses (3 gram/day or 6 gram/day) for 1-2 weeks. In the other sub-study patients were treated with a progressive dose regimen—in sequence: 0.75 gram/day for one week, 1.5 gram/day for one week, and 3 gram/day for one week. On completion, patients were eligible for enrollment in S245.3.103. The uncontrolled nature of this study precluded substantive review of efficacy; however design allowed for assessment of AEs. Forty three patients received placebo, and 41 patients received Creon MMS.

The 1-Week Adult PEI Study (S245.3.104) was a 4 week OL study of Creon MMS in 85 adults with PEI due to CP or PY, and other, non-specified, causes of pancreatic insufficiency. After a 5-day, open-label placebo treatment period, patients received 4 weeks of open-label treatment with Creon MMS. The uncontrolled nature of this study precluded substantive review of efficacy; however design allowed for assessment of AEs. Eight-five patients received placebo and 83 patients received Creon MMS. On completion, patients were eligible for enrollment in S245.3.103.

There were 162 individual patients in the safety set from the above studies. No SAE was counted more than once due to enrollment in more than one of the three studies. Patients who enrolled in the Long Term PEI Exposure study after enrollment in either of the two other studies were assigned new unique patient identifiers. The final number of unique patient identifiers (hereafter, patients) is 187. One hundred eighty seven patients received Creon MMS and 128 patients received placebo.

SAEs were reported in 11% of the 187 patients. The most common SAEs by SOC were gastrointestinal disorders, infections and infestations, and neoplasm. The most common SAEs b PT were vomiting (1.6% of patients), and nausea, liver abscess, liver metastasis, and recurrent pancreatic carcinoma (each reported in 1% of patients). Of note, there were no treatment emergent SAEs (TE-SAEs) in the PEI Dose Comparison Study. These findings are summarized in 54 below.

Table 54: SAEs in Patients Receiving MMS In Three Non-integrated Studies

All patients in safety set who received MMS, N=187		Events	N	%
		31	20	11
SOC	Preferred Term			
Cardiac disorders	Pulmonary edema NOS	1	1	0.5
Gastrointestinal disorders	Vomiting NOS	3	3	1.6
	Nausea	2	2	1
	Pancreatitis acute on chronic	2	1	0.5
	Abdominal pain upper	1	1	0.5
	Diarrhea NOS	1	1	0.5
	Ileus paralytic	1	1	0.5
General disorders and administration site conditions	Malaise	1	1	0.5
	Pyrexia	1	1	0.5
Hepatobiliary disorders	Hepatic function abnormal NOS	1	1	0.5
Infections and infestations	Liver abscess	2	2	1
	Enterocolitis infectious	1	1	0.5
	Influenza	1	1	0.5
	Sepsis NOS	1	1	0.5
Injury, poisoning and procedural complications	Brain contusion	1	1	0.5
	Fractured pelvis NOS	1	1	0.5
Metabolism and nutrition disorders	Malnutrition NOS	2	1	0.5
Musculoskeletal and connective tissue disorders	Back pain aggravated	1	1	0.5
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Metastases to liver	2	2	1
	Pancreatic carcinoma recurrent	2	2	1
	Metastases to lung	1	1	0.5
Renal and urinary disorders	Hematuria	1	1	0.5
Respiratory, thoracic and mediastinal disorders	Epistaxis	1	1	0.5

Except for one patient with hypoglycemia not otherwise specified, there were no SAEs in the placebo treated group,; therefore, the placebo column is not shown.

The frequency of SAEs in the non-integrated long term studies was 11% for any SAE and between 0.5 and 1.6% for SAEs classified by PT. The most common SAEs in the long-term studies were vomiting (1.6%), nausea (1%), and pancreatitis (1%); primary, recurrent, or metastatic carcinoma (0.5 to 1%); infections and infestations (0.5 to 1%); and liver abscess (1%). The carcinoma SAEs all reflect entry diagnoses.

This reviewer concluded the SAEs reported in these three studies reflect pre-existing enrollment diagnoses, and do not differ substantially to SAEs reported in the ISS. The relatively common finding of carcinoma is related to baseline diagnoses and is not thought by this reviewer to be related to medication effects

10.1.5 Additional Tables

Table 55: All Dropouts listed in ISS, by Drug or Placebo Treatment

All Patients who dropped out by treatment group		All Patients (N=1,546)		MMS (N=594)		MS (N=991)		Placebo (N=589)	
		N	%	N	%	N	%	N	%
		53	3.4	14	2.4	19	1.9	17	2.9
Listing of Individual AEs									
SOC	Preferred Term	N	%	N	%	N	%	N	%
Blood and lymphatic system disorders	Iron deficiency anemia	1	0.1	0	0	0	0	1	0.2
Cardiac disorders	Cardiac failure	2	0.1	0	0	1	0.1	1	0.2
	Acute myocardial infarction	1	0.1	0	0	0	0	1	0.2
	Cardiovascular disorder	1	0.1	0	0	0	0	1	0.2
Ear and labyrinth disorders	Ear pain	1	0.1	0	0	0	0	1	0.2
	Vertigo	1	0.1	0	0	0	0	1	0.2
Endocrine disorders	Hyperthyroidism	1	0.1	0	0	0	0	1	0.2
Gastrointestinal disorders	Abdominal pain	10	0.7	6	1.0	3	0.3	1	0.2
	Diarrhea	7	0.5	4	0.7	2	0.2	1	0.2
	Nausea	7	0.5	3	0.5	4	0.4	0	0
	Vomiting	7	0.5	2	0.3	4	0.4	1	0.2
	Abdominal pain upper	3	0.2	0	0.0	2	0.2	1	0.2
	Constipation	2	0.1	1	0.2	1	0.1	0	0
	Flatulence	2	0.1	2	0.3	0	0.0	0	0
	Abdominal discomfort	1	0.1	1	0	0	0.0	0	0
	Abdominal distension	1	0.1	1	0	0	0.0	0	0
	Distal intestinal obstruction syndrome	1	0.1	1	0	0	0.0	0	0
	Frequent bowel movements	1	0.1	1	0	0	0.0	0	0
	Pancreatic pseudocyst	1	0.1	0	0	1	0.1	0	0
	Pancreatitis	1	0.1	0	0	0	0.0	1	0.2
	Pancreatitis acute	1	0.1	0	0	0	0.0	1	0.2
	Pancreatitis chronic	1	0.1	0	0	1	0.1	0	0
	Rectal hemorrhage	1	0.1	0	0	1	0.1	0	0
General disorders and administration site conditions	Drug withdrawal syndrome	1	0.1	0	0	1	0.1	0	0
	General symptom	1	0.1	0	0	0	0	1	0
	Heparin-induced thrombocytopenia	1	0.1	0	0	0	0	1	0
	Influenza like illness	1	0.1	0	0	1	0.1	0	0
	Pain	1	0.1	0	0	1	0.1	0	0
Infections and infestations	Superinfection lung	2	0.1	0	0	0	0	2	0.3
	Appendiceal abscess	1	0.1	1	0	0	0.0	0	0
	Respiratory tract infection	1	0.1	0	0	1	0.1	0	0
	Sinusitis	1	0.1	0	0	0	0	1	0.2
	Urinary tract infection	1	0.1	0	0	1	0	0	0.0
Investigations	Blood thyroid stimulating hormone decreased	1	0.1	0	0	0	0	1	0.2

Table 55: All Dropouts listed in ISS, by Drug or Placebo Treatment

All Patients who dropped out by treatment group		All Patients (N=1,546)		MMS (N=594)		MS (N=991)		Placebo (N=589)	
		N	%	N	%	N	%	N	%
		53	3.4	14	2.4	19	1.9	17	2.9
Listing of Individual AEs									
SOC	Preferred Term	N	%	N	%	N	%	N	%
Metabolism and nutrition disorders	Dehydration	3	0.2	0	0	3	0.3	0	0
	Hypoglycemia	2	0.1	0	0	1	0.1	1	0.2
	Hyperglycemia	1	0.1	0	0	1	0.1	0	0
	Ketoacidosis	1	0.1	0	0	1	0.1	0	0
	Malnutrition	1	0.1	0	0	1	0.1	0	0
Musculoskeletal and connective tissue disorders	Muscle spasms	2	0.1	2	0.3	0	0	0	0
Nervous system disorders	Dizziness	1	0.1	1	0.2	0	0	0	0
	Headache	1	0.1	0	0	0	0	1	0.2
	Syncope	1	0.1	0	0	0	0	1	0.2
	Tremor	1	0.1	1	0.2	0	0	0	0
Psychiatric disorders	Abnormal behavior	1	0.1	0	0	0	0	1	0.2
Renal and urinary disorders	Renal failure	1	0.1	1	0.2	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Cough	2	0.1	2	0.3	0	0	0	0
	Increased bronchial secretion	1	0.1	1	0.2	0	0	0	0
	Respiratory failure	2	0.1	1	0.2	0	0	1	0.2
	Acute respiratory failure	1	0.1	0	0	0	0	1	0.2
	Dyspnea	1	0.1	1	0.2	0	0	0	0
	Hyperventilation	1	0.1	1	0.2	0	0	0	0
	Productive cough	1	0.1	1	0.2	0	0	0	0
	Pulmonary edema	1	0.1	0	0	0	0	1	0.2
Surgical and medical procedures	Surgery	1	0.1	0	0	1	0.1	0	0
Vascular disorders	Aneurysm ruptured	1	0.1	0	0	1	0.1	0	0
	Shock	1	0.1	1	0.2	0	0	0	0

Table 56: All SAEs reported in the ISS

SAEs Occurring any Patient Reported in the ISS		Total (N=1,546)		MMS (N=594)		MS (N=991)		Other PEP[1] (N=311)		Placebo (N=589)	
		N	%	N	%	N	%	N	%	N	%
		95	6.1	20	3.4	48	4.8	5	1.3	21	3.4
SOC	**Preferred Term**	**Listing of Individual SAEs**									
Blood and lymphatic system disorders	Anemia	1	0.1	1	0.2	0	0	0	0	0	0
Cardiac disorders	Cardiac failure	2	0.1	0	0	1	0.1	0	0	1	0.2
	Acute myocardial infarction	1	0.1	0	0	0	0	0	0	1	0.2
	Atrial tachycardia	1	0.1	1	0.2	0	0	0	0	0	0
	Cardiovascular disorder	1	0.1	0	0	0	0	0	0	1	0.2
	Right ventricular failure	1	0.1	1	0.2	0	0	0	0	0	0
Gastrointestinal disorders	Abdominal pain	7	0.5	1	0.2	5	0.5	0	0	1	0.2
	Vomiting	4	0.3	1	0.2	3	0.3	0	0	0	0
	Nausea	3	0.2	0	0	3	0.3	0	0	0	0
	Pancreatitis acute	2	0.1	0	0	0	0	0	0	2	0.3
	Pancreatitis chronic	2	0.1	0	0	2	0.2	0	0	0	0
	Abdominal pain upper	1	0.1	0	0	1	0.1	0	0	0	0
	Acute abdomen	1	0.1	1	0.2	0	0	0	0	0	0
	Diarrhea	1	0.1	1	0.2	0	0	0	0	0	0
	Distal intestinal obstruction syndrome	1	0.1	1	0.2	0	0	0	0	0	0
	Gastrointestinal disorder	1	0.1	1	0.2	0	0	0	0	0	0
	Gastroesophageal reflux disease	1	0.1	1	0.2	0	0	0	0	0	0
	Impaired gastric emptying	1	0.1	1	0.2	0	0	0	0	0	0
	Intestinal obstruction	1	0.1	0	0	0	0	1	0.3	0	0
	Intussusception	1	0.1	1	0.2	0	0	0	0	0	0
	Meconium ileus	1	0.1	1	0.2	0	0	0	0	0	0
	Melena	1	0.1	0	0	0	0	0	0	1	0.2
	Pancreatic pseudocyst	1	0.1	0	0	1	0.1	0	0	0	0
	Pancreatitis	1	0.1	0	0	0	0	0	0	1	0.2
	Stomatitis	1	0.1	1	0.2	0	0	0	0	0	0
General disorders and administration site conditions	Pyrexia	7	0.5	4	0.7	2	0.2	0	0	1	0.2
	Pain	2	0.1	0	0	1	0.1	1	0.3	0	0
	Cyst	1	0.1	0	0	1	0.1	0	0	0	0
	Drug withdrawal syndrome	1	0.1	0	0	1	0.1	0	0	0	0
	Heparin-induced thrombocytopenia	1	0.1	0	0	0	0	0	0	1	0.2
	Edema	1	0.1	0	0	0	0	0	0	1	0.2
Infections and infestations	Bronchitis acute	3	0.2	2	0.3	1	0.1	0	0	0	0
	Pneumonia[1]	8	0.5	1	0.2	6	0.6	0	0	0	0
	Superinfection lung	3	0.2	0	0	0	0	0	0	3	0.5
	Influenza	2	0.1	1	0.2	0	0	1	0.3	0	0
	Lower respiratory tract infection	2	0.1	2	0.3	0	0	0	0	0	0
	Urinary tract infection	2	0.1	0	0	2	0.2	0	0	0	0
	Acute tonsillitis	1	0.1	0	0	1	0.1	0	0	0	0

Table 56: All SAEs reported in the ISS

SAEs Occurring any Patient Reported in the ISS		Total (N=1,546)		MMS (N=594)		MS (N=991)		Other PEP[1] (N=311)		Placebo (N=589)	
		N	%	N	%	N	%	N	%	N	%
		95	6.1	20	3.4	48	4.8	5	1.3	21	3.4
SOC	**Preferred Term**	**Listing of Individual SAEs**									
	Appendiceal abscess	1	0.1	1	0.2	0	0	0	0	0	0
	Herpes virus infection	1	0.1	1	0.2	0	0	0	0	0	0
	Infection	1	0.1	0	0	1	0.1	0	0	0	0
	Lung infection pseudomonal	1	0.1	1	0.2	0	0	0	0	0	0
	Nasopharyngitis	1	0.1	0	0	1	0.1	0	0	0	0
	Pseudomonas infection	1	0.1	0	0	1	0.1	0	0	0	0
	Respiratory tract infection	1	0.1	0	0	1	0.1	0	0	0	0
	Sepsis	1	0.1	0	0	0	0	0	0	1	0.2
	Sinusitis	1	0.1	0	0	1	0.1	0	0	0	0
Injury, poisoning and procedural complications	Femoral neck fracture	1	0.1	0	0	1	0.1	0	0	0	0
	Injury	1	0.1	0	0	0	0	0	0	1	0.2
	Near drowning	1	0.1	0	0	1	0.1	0	0	0	0
	Subdural hematoma	1	0.1	0	0	0	0	0	0	1	0.2
Metabolism and nutrition disorders	Hypoglycemia	5	0.3	0	0	2	0.2	0	0	3	0.5
	Dehydration	3	0.2	0	0	3	0.3	0	0	0	0
	Hyperglycemia	1	0.1	0	0	1	0.1	0	0	0	0
	Ketoacidosis	1	0.1	0	0	1	0.1	0	0	0	0
	Malnutrition	1	0.1	0	0	1	0.1	0	0	0	0
Musculoskeletal and connective tissue disorders	Back pain	2	0.1	1	0.2	0	0	0	0	1	0.2
	Neck pain	1	0.1	0	0	0	0	0	0	1	0.2
Nervous system disorders	Dizziness	1	0.1	0	0	0	0	0	0	1	0.2
	Hypoglycemic coma	1	0.1	0	0	0	0	0	0	1	0.2
	Metabolic encephalopathy	1	0.1	1	0.2	0	0	0	0	0	0
	Migraine	1	0.1	0	0	0	0	0	0	1	0.2
	Syncope	1	0.1	0	0	0	0	0	0	1	0.2
Psychiatric disorders	Anxiety	1	0.1	0	0	1	0.1	0	0	0	0
	Depression	1	0.1	0	0	1	0.1	0	0	0	0
	Suicide attempt	1	0.1	0	0	0	0	1	0.3	0	0
Renal and urinary disorders	Renal failure	1	0.1	1	0.2	0	0	0	0	0	0
	Renal impairment	1	0.1	1	0.2	0	0	0	0	0	0
Reproductive system and breast disorders	Testicular torsion	1	0.1	1	0.2	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Cough	3	0.2	3	0.5	0	0	0	0	0	0
	Lung disorder	8	0.5	1	0.2	7	0.7	0	0	0	0
	Bronchial obstruction	2	0.1	2	0.3	0	0	0	0	0	0
	Hemoptysis	2	0.1	1	0.2	1	0.1	0	0	0	0
	Productive cough	2	0.1	2	0.3	0	0	0	0	0	0
	Respiratory failure	2	0.1	1	0.2	0	0	0	0	1	0.2
	Acute respiratory failure	1	0.1	0	0	0	0	0	0	1	0.2
	Bronchospasm	1	0.1	0	0	1	0.1	0	0	0	0
	Dyspnea	1	0.1	1	0.2	0	0	0	0	0	0
	Pharyngolaryngeal pain	1	0.1	1	0.2	0	0	0	0	0	0

Table 56: All SAEs reported in the ISS

SAEs Occurring any Patient Reported in the ISS		Total (N=1,546)		MMS (N=594)		MS (N=991)		Other PEP[1] (N=311)		Placebo (N=589)	
		N	%	N	%	N	%	N	%	N	%
		95	6.1	20	3.4	48	4.8	5	1.3	21	3.4
SOC	**Preferred Term**	**Listing of Individual SAEs**									
	Pulmonary edema	1	0.1	0	0	0	0	0	0	1	0.2
	Respiratory disorder	1	0.1	0	0	1	0.1	0	0	0	0
	Tachypnea	1	0.1	1	0.2	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	Cold sweat	1	0.1	0	0	0	0	0	0	1	0.2
Surgical and medical procedures	Surgery	2	0.1	0	0	2	0.2	0	0	0	0
	Gastrostomy tube insertion	1	0.1	1	0.2	0	0	0	0	0	0
	Hospitalization	1	0.1	0	0	0	0	1	0.3	0	0
	Limb operation	1	0.1	0	0	1	0.1	0	0	0	0
	Respiratory therapy	1	0.1	0	0	1	0.1	0	0	0	0
Vascular disorders	Aneurysm ruptured	1	0.1	0	0	1	0.1	0	0	0	0
	Shock	1	0.1	1	0.2	0	0	0	0	0	0

[1]One of eight patients with SAE categorized as pneumonia was in the post-treatment period > 14 days after last dose of drug or placebo.
[2] Table does not include six non-treatment emergent SAEs which occurred in 3 patients during the pre-treatment period. These SAEs included three upper respiratory tract infections in one person reported on the same day; one cough in one person; one episode of acute otitis media in one person; and one episode of salmonella gastroenteritis.
[3] Including Cotazym, Pancrease, Pancrex, and Panzytrat commercial PEPs

Table 57: AEs in ≥ 1% of Patients Where Seriousness was listed as Unknown

All AEs; Unknown Seriousness		Total (N=406)		MS (N=276)		Other PEPs (N=125)		Placebo (N=131)	
		N	%	N	%	N	%	N	%
		187	46	143	52	74	59	21	16
AEs in ≥ 1% of patients									
SOC	Preferred Term								
Gastrointestinal	Abdominal pain	58	14	32	12	25	23	1	1
	Diarrhea	38	9	23	8	13	18	2	2
	Vomiting	35	9	19	7	13	16	3	2
	Abnormal feces	26	6	13	5	13	21	0	0
	Nausea	20	5	11	4	5	6	4	3
	Abdominal distension	10	3	5	2	5	4	0	0
	Abdominal pain upper	11	3	5	2	6	6	0	0
	Constipation	8	2	3	1	5	6	0	0
	Flatulence	4	1	2	1	2	2	0	0
	Hematochezia*	3	1	3	1	0	0	0	0
General and administration site	Pyrexia	17	4	12	4	5	4	0	0
	Pain	12	3	8	3	2	2	2	2
	Malaise	10	3	6	2	4	4	0	0
Infections and infestations	Nasopharyngitis	17	4	14	5	3	2	0	0
	Rhinitis	16	4	12	4	4	5	0	0
Metabolism and nutrition	Anorexia	12	3	6	2	6	5	0	0
Nervous system	Headache	26	6	15	5	7	13	2	2
Respiratory, thoracic and mediastinal	Cough	47	12	35	13	12	11	0	0
	Lung disorder	17	4	10	4	7	6	0	0
	Productive cough	11	3	9	3	2	2	0	0

[1]AE=Non serious AEs and AEs of unknown seriousness
[2] N=Number of persons experiencing events.
[3] Population: Total patients in (1) studies where seriousness assessment was not planned and (2) studies wherein seriousness was not assigned to at least one AE.
* AE > 1% in subgroup.

Table 58: Multiple Dose studies, electronically reproduced from Sponsor's table 8.8.1; Vol. 26, p 9485-7

Study	N			Blind	Design	Duration of Tx	Drug (Duration)	Control/Other Drug	Remarks
	1	2	3						
Cystic Fibrosis with PEI									
223.8.01	33	-	33 (32)	Open	2-CO	5 weeks	MS 25000 (2 wks)	MS 8000 (2 wks)	1 week run-in with MS 8000
K.224.5001	89	-	89	DB	2-CO	8 weeks	MS 25000 (4 wks)	Panzytrat 20000 (4 wks)	
K.224.5006	46	-	45	Open	S	26 weeks	MS 25000 (13 wks)	Pancrease 5000, MS 8000 (13 wks)	Pancrease 5000 or MS 8000 during Phase 1 and MS 25000 during Phase 2
K.224.5010	18	-	14	Open	2-CO	6-10 weeks	MS 25000 (2 wks)	Cotazym Forte (2 wks)	2-6 weeks run-in with Cotazym Forte
K.245.5002	69	69	69	Open	2-CO	4 weeks	MMS 10000 (2 wks)	MS 12000 (2 wks)	
K.245.5004	34	33	34 (33)	DB	2-CO	7 weeks	MMS 10000 (2 wks)	MS 8000 (2 wks)	3 weeks run-in with MS 8000
KREON.586	27	-	27	DB	2-CO	10 weeks	MS 8000 (4 wks)	Pancrease 5000 (4 wks)	2 weeks run-in with MS 8000
KREON 84/02	20	-	20	DB	2-CO	8 weeks	MS 8000 (4 wks)	Pancrex V Forte 5600 (4 wks)	
KREON 84/03	21	-	21	Open	2-CO	8 weeks	MS 8000 (4 wks)	Pancrex V Forte 5600 (4 wks)	
KREO.584	29	-	29	Open	S	104 weeks	MS 8000 (104 wks)	-	
KREO.592	17	-	17	Open	2-CO	12 weeks	MS 8000 (6 wks)	MS 8000 (6 wks)	capsules versus sachets
KREO.629 *	11	11	-	SB	S	12 days	MMS 10000 (6 days)	Placebo (6 days)	
KREO.636	64	-	63	Open	2-CO	2 weeks	MS 8000 (1 wk)	Pancrease (1 wk)	
RR.1044-01	21	-	21	Open	2-CO	4 weeks	MS 8000 (2 wks)	Pancrease (2 wks)	
S223.3.101	47	47 (18)	-	DB	2-PG	2-3 weeks	MMS 20000 (1 wk)	Placebo (1 wk)	1-2 weeks run-in with MMS 20000
S223.3.102	50	50 (18)	-	DB	2-PG	2-3 weeks	MMS 20000 (6 days)	Placebo (6 days)	1-2 weeks run-in with MMS 20000
S245.3.105	59	57	59 (55)	Open	2-CO	10 weeks	MMS 10000 (4 wks)	MS 8000 (4 wks)	2 weeks run-in with MS 8000
S245.3.117 *	3	3	-	Open	S	not fixed	MMS 10000	-	The sachets administered contained 20000 lipase units of Creon MMS 10000. Max trtmt duration before cut-off: > 4 yrs
S245.3.118 *	40	40	-	Open	2-CO	30 days	Creon for children	MMS 12000 (15 days)	

Table 58: Multiple Dose studies, electronically reproduced from Sponsor's table 8.8.1; Vol. 26, p 9485-7

Study	N			Blind	Design	Duration of Tx	Drug (Duration)	Control/Other Drug	Remarks
	1	2	3						
							(MMS) (15 days)		
S248.3.002	33	29	33 (29)	DB	2-CO	7 weeks	MMS 25000 (2 wks)	MS 25000 (2 wks)	3 weeks run-in with MS 25000
S248.3.003 *	12	12	-	Open	S	8 weeks	Creon for children (MMS) (8 wks)	-	
Chronic Pancreatitis with PEI									
223.2.01	27	13	-	DB	2-PG	4 weeks	MMS 10000 (2 wks)	Placebo (2 wks)	2 wks run-in with placebo
CREO.635 *	20	-	19	DB	2-CO	4 weeks	MS 8000 (2 wks)	Placebo (2 wks)	
K.224.5003	11	-	11	DB	2-CO	5 weeks	MS 25000 (2 wks)	Pancrease 6200 (2 wks)	1 wk run-in with Pancrease
K.224.5008	6	-	6	Open	S	3 weeks	MS 25000 (2 wks)	-	1 wk run-in with placebo
K.224.5009	24	-	24	DB	2-CO	20 days	MS 25000 (10 days)	Pancrease (10 days)	
K.224.5016	65	-	64	DB	2-CO	5 weeks	MS 25000 (2 wks)	MS 8000 (2 wks)	1 wk run-in with placebo
K.245.5003	37	23	28 (23)	DB	2-CO	7 weeks	MMS 10000 (2 wks)	MS 10000 (3 wks)	1 wk run-in with placebo and 1 wk with MS 10000
K.245.5005	40	17	39	DB	2-PG	4 weeks	MMS 10000 (2 wks)	Placebo (2 wks)	1 wk run-in with placebo and 1 wk with MS 10000
KREO.628	31	-	30	DB	3-CO	12 weeks	MS 10000 (8 wks)	Placebo (4 wks)	
RR.1044-03	58	-	57	DB	2-CO	8 weeks	MS 8000 (4 wks)	Placebo (4 wks)	
S245.3.107 *	3	4	-	DB	2-CO	4 weeks	MMS 10000 (1 wk)	Placebo (1 wk)	1w run-in with placebo and 1 wk with MMS 10000
S245.3.115-CP*	35	23		DB	3-PG	7 days	MMS 10000 (1 wk) (two dose groups)	Placebo (1 wk)	The sachets contained 20000 lipase units of Creon MMS 10000. The study included patients with CP and patients with PY. Only patients with CP are counted here
Pancreatectomy with PEI									
K.224.5002	40	-	40 (39)	DB	2-CO	6 wks	MS 25000 (2 wks)	MS 8000 (2 wks)	2 wks run-in with MS 8000, Pancreatectomy
RK.223.00.02	16	-	16 (7)	DB	2-PG	8 wks	MS 8000 (4 wks)	Placebo (4 wks)	4 wks run-in with MS 8000, Pancreatectomy
S248.3.001	27	21	27	DB	2-CO	6 wks	MMS 25000	MS 8000 (2	2 wks run-in with MS

Table 58: Multiple Dose studies, electronically reproduced from Sponsor's table 8.8.1; Vol. 26, p 9485-7

Study	N			Blind	Design	Duration of Tx	Drug (Duration)	Control/Other Drug	Remarks
	1	2	3						
			(21)				(2 wks)	wks)	8000, Pancreatectomy
S245.3.102	11	3	9	DB	2-PG	4 wks	MMS 20000 (2 wks)	Placebo (2 wks)	1 wk run-in with placebo and 1 wk with MS 10000, Gastrectomy
S245.3.115-PY*	59	41	-	DB	3-PG	7 days	MMS 10000 (1 wk) (two dose groups)	Placebo (1 wk)	1w run-in with placebo. The sachets contained 20000 lipase units of Creon MMS 10000. The study included patients with CP and patients with PY. Only patients with PY are counted here.
Acute Pancreatitis with PEI									
S248.4.001 *	56	27	-	DB	2-PG	26-30 days	MMS 25000 (26-30 days)	Placebo (26-30 days)	
S248.4.002 *	21	10	-	DB	2-PG	84 days	MMS 25000 (84 days)	Placebo (84 days)	
Diabetes Mellitus with PEI									
S245.3.112	6	3	-	DB	2-PG	7 days	MMS 10000 (7 days)	Placebo (7 days)	
S245.3.113	23	13	-	DB	2-PG	7 days	MMS 10000 (7 days)	Placebo (7 days)	
Diabetes Mellitus without PEI									
S245.3.110	80	39	-	DB	2-PG	16 wks	MMS 10000 (16 wks)	Placebo (16 wks)	
HIV without PEI									
S245.3.116*	10	6	-	DB	2-PG	4 wks	MMS 10000 (4 wks)	Placebo (4 wks)	
Chronic Malnutrition in the Elderly without PEI									
CREO.630 *	52	-	26	DB	2-PG	90 days	MS 12000 (90 days)	Placebo (90 days)	
CREO.631 *	44	-	21	DB	2-PG	90 days	MS 12000 (90 days)	Placebo (90 days)	

* Newly integrated since NDA Update 2002
Blind: DB=double-blind SB=single-blind Open=open-label Test/control drug: MS = Creon microspheres, MMS = Creon minimicrospheres
Design: PG=parallel groups CO=cross-over (the preceding number is the number of treatments) S=single treatment/sequential design
N: (1) = number of patients randomized
(2) = number of patients who took Creon MMS (first number includes run-in, second number not)
(3) = number of patients who took Creon MS (first number includes run-in, second number not)

Table 59, Single Dose studies, electronically reproduced from Sponsor's table 8.8.1; Vol. 26, p 9489

Indication	N			Blind	Design	Duration of Treatment	Test Drug (Duration)	Control/Other Drug
	1	2	3					
Cystic Fibrosis with PEI								
S245.3.111	21	20	-	Open	3-CO	single dose	MMS 10000	Pancrease, Placebo
S245.4.004^	12	12	-	DB	3-CO, 4 trtmt	single dose	MMS 5000, 15000, 40000	Placebo
S248.2.001^	11	11		Open	S	single dose	MMS 25000	-
Chronic Pancreatitis with PEI								
K.224.5011^	5	5	-	DB	2-CO	single dose	MMS 25000	Placebo
S245.2.003	14	14	-	DB	2-CO	single dose	MMS 12000	MMS 10000

^ Study report presented to FDA in 2002
Blind: DB=double-blind SB=single-blind Open=open-label Test/control drug: MS = Creon microspheres, MMS = Creon minimicrospheres
Design: PG=parallel groups CO=cross-over (The preceding number is the number of CO periods. The number of treatments (trtmt) is given if different from the number of CO periods)
S=single treatment/sequential design
N: (1) = number of patients randomized
(2) = number of patients who took Creon MMS
(3) = number of patients who took Creon MS

Table 59: Table of studies not integrated due to data integrity issues; electronically copied from the Sponsor's submission (Volume 26, page 9490)

		N						
Study Code	1	2	3	Blind	Design	Duration of Treatment	Test Drug (Duration)	Control/Other Drug
K.245.5703	26 (17)	24 (17)	--	Open	2-PG S	1-2 weeks 3 weeks	MMS 10000 (1-2 wks) (two dose groups) MMS 10000 (3 wks) (three doses sequentially, 1 wk for each)	5 days run-in with placebo were followed by a period with two parallel dose groups, which was then followed by a period during which three doses were given sequentially. The numbers in the second line refer to the latter period. The study included both patients with CP and patients with pancreatectomy.
S245.3.103	63	63	--	Open	S	24-52 weeks	MMS 10000 (24-52 wk)	Partly extended from S245.3.104. The study included patients with CP, patients with pancreatectomy, and patients with gastrectomy.
S245.3.104	85	83	-	Open	S	4 weeks	MMS 10000 (4 wk)	5 days run-in with placebo.
								The study included patients with CP, patients with pancreatectomy, and patients with gastrectomy.
S245.2.002	5	5	-	Open	S	53 weeks	MMS 10000 (53 wk)	5 days run-in with placebo
								The study included patients with CF.
S245.4.007	45	unk (4)	unk (4)	DB	2-PG	6 months	MMS 25000 (6 months)	Placebo (6 months), still blinded. Patients with gastrectomy.
S245.3.119	38	38	-	DB	2-CO	4 wks	MMS 25000 (2 wks)	Placebo (2 wks), not reported by cut-off date. HIV patients.
Laugier	26	26	-	DB	2-PG	6 months	MS 12000	No full study report available. Patients with chronic pancreatitis.

Blind: DB=double-blind SB=single-blind Open=open-label Test/control drug: MS = Creon microspheres, MMS = Creon minimicrospheres
Design: PG=parallel groups CO=cross-over (The preceding number is the number of CO periods. The number of treatments (trtmt) is additionally given if different from the number of CO periods)
S=single treatment/sequential design
N: (1) = number of patients randomized, (2) = number of patients who took Creon MMS, (3) = number of patients who took Creon MS,
(4) unknown because the study was still blinded

10.2 References

1 Borowitz, DS; Grand, RJ; Durie, PR; Consensus Committee (sup A). Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. J Pediatrics. 127(5), Nov 1995, pp 681-684. (PMID: 7472816)

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Review of this bridging study was addressed in a prior NDA review cycle (2007)

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M E M O R A N D U M

DATE: February 13, 2008

FROM: Felicia Collins, MD, MPH, Medical Officer
Pediatric and Maternal Health Staff, Office of New Drugs

THROUGH: Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

TO: Daniel Shames, MD, Acting Director
Division of Gastroenterology Products,
Office of Drug Evaluation III, Office of New Drugs

RE: Creon® formulations for pediatric patients

Drug: Creon® (pancrelipase) [pancreatic enzyme product]
Dosage Form: Delayed-release capsules
(6,000, 12,000, and 24,000 USP units of lipase)
Administration Route: Oral
Sponsor: Solvay Pharmaceuticals, Inc.
Indication: (proposed) for adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency
Application: NDA 20-725 (document date December 14, 2007)

Division's Consult Comments

The Division of Gastroenterology Products [Division] is seeking advice from the [Pediatric and Maternal Health Staff] PMHS regarding the development of pediatric formulations for Creon® (pancrelipase delayed-release capsules) and other pancreatic enzyme products (PEPs) that would be suitable for administration to pediatric patients unable to swallow PEP capsules.

Questions:

1) [Pediatric Research Equity Act] PREA regulations state that age-appropriate formulations must be developed and tested in the pediatric population for products

that will be used in children. Do you feel that the current practice of breaking open capsules, approximating the dose, and administering PEPs sprinkled on food is adequate and consistent with PREA and that the PEPs may be safely administered in this manner?

2) If the response to number 1 is no, do pediatric formulations for PEPs need to be developed, and should this be a condition of approval for all PEPs intended for use in children? Do you have any specific recommendations for the development of these pediatric formulations?

3) Do you have any additional comments or recommendations?

Materials Reviewed

- Division's consult background information, January 11, 2008
- Sponsor's meeting background package (including proposed drug labeling), December 14, 2007
- FDA Guidance on Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs, April 2006
- Pub Med

Background

Product Description

According to the Sponsor's proposed draft labeling, Creon® (pancrelipase) is an extract of porcine pancreatic glands that can serve as a replacement for lacking physiologically secreted pancreatic enzymes. Creon's® major enzyme components are lipase, free proteases, and α-amylase, and these pancreatic enzymes are enteric-coated to resist gastric destruction or inactivation. When Creon® is taken orally, the pancreatic enzymes catalyze the hydrolysis of fats to monoglycerol, glycerol and fatty acids; protein into peptides and amino acids; and starch into dextrins and short chain sugars. The Sponsor has requested marketing approval for Creon® capsules in three doses corresponding to 6,000, 12,000, and 24,000 USP units of lipase.

Regulatory History

Pancreatic Enzyme Products

The Division has provided the following regulatory history regarding pancreatic enzyme products.

> PEPs have been widely available in the US since prior to the Federal Food, Drug, and Cosmetic Act of 1938, and there is a large amount of clinical experience with these products. However, most PEPs have been available since pre-Drug Efficacy Study Implementation (DESI, pre-1962) and have never undergone formal evaluation for efficacy or safety under investigational new drug applications (INDs) or new drug applications (NDAs).
>
> In 2004, a Federal Register (FR) Notice was published stating that all PEPs must get NDA approval within the next four years (deadline April 28, 2008). To be approved, PEP NDAs must meet the requirements for content and format of an application as stated in 21CFR 314.50. The long-term safety and

> efficacy of PEPs in pediatric patients have been demonstrated by the long and extensive clinical experience with these products that has documented better growth and nutritional status, lower mortality, and lower morbidity in cystic fibrosis (CF) patients. Thus, sponsors only have been asked to demonstrate short-term safety and efficacy in support of their NDA clinical development programs, typically in 1 to 2 week clinical trials that demonstrate the clinical effects of these products on markers such as increased fat absorption in stool collections. The deadline [for NDA approval] was later extended to April 28, 2010 as many manufacturers were experiencing delays in complying with all NDA regulations, especially those for manufacturing.

In April 2006, the FDA Guidance entitled *Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs*, noted that

> to comply with PREA, PEP NDAs must contain data that are adequate to assess the safety and effectiveness of the PEP for the claimed indication in each of the appropriate pediatric subgroups (newborns, infants, children, and adolescents). The data should be adequate to support dosing and administration in each pediatric subpopulation for which the drug has been assessed. Because solid dosage forms of PEPs cannot be swallowed by young pediatric patients (i.e., generally 6 years of age or younger), under PREA, sponsors must attempt to develop age-appropriate formulations for this patient population.

Creon®

The Division has provided the following regulatory history regarding Creon®.

> Since approximately the 1970's, Creon® has been available in the US during which time it reportedly has been used by both adult and pediatric patients.
>
> On July 31, 1991, the Sponsor submitted its original NDA for Creon®. The application was placed under the Application Integrity Policy (AIP) on September 24, 1997 for data integrity issues, and review of the NDA was suspended. On April 9, 2003, the AIP status was revoked and review of the NDA resumed. On October 9, 2003, the Division issued a NDA Not Approvable (NA) letter. On November 17, 2006, the Division received the Sponsor's Complete Response (CR) to the NA action.
>
> On August 16, 2007, the Division issued an Approvable (AE) letter, in which the outstanding issues mainly were related to CMC concerns. However, the AE letter included a clinical note that the intended-to-be-marketed product (TbMP) had not been evaluated in clinical trials, and the Sponsor had been unable to link the currently marketed product (CMP) with the TbMP [via Bridging Study S245.2.003]. Therefore, the Division stated the Sponsor must conduct at least one clinical study with the TbMP as part of the CR to the AE action.
>
> Consequently, the Sponsor is currently performing two studies with the TbMP: (1) a study in CF patients ≥ 12 years old (Study S245.3.126 with a target N=26); and (2) a study in adults with chronic pancreatitis or

pancreatectomy (target N=approximately 46 – 52). If the CF study, which is expected to be completed first, provides substantial evidence of safety and efficacy in children ≥ 12 years old, the Division might consider extrapolating efficacy down to a portion of the remaining pediatric population (exact age would need to be internally discussed), but there still would not be any safety data with the TbMP in children < 12 years old. Of note, prior studies in children 1 to 24 months old have been conducted with the CMP, but they cannot be used to support efficacy or safety of the TbMP in infants.

On January 17, 2008, the Division met with the Sponsor to provide guidance on several issues outlined in the AE letter. During this meeting, the Division requested that the Sponsor submit a pediatric plan for studies in the younger patients, and the Sponsor has agreed to do this.

Ultrase® and Other PEPs

The Division has provided the following regulatory history regarding Ultrase® and other PEPs.

Ultrase®, another enteric coated PEP that is administered to pediatric patients with CF, is currently under NDA review (NDA 22-222). The Ultrase® Sponsor also has proposed that this PEP be administered to pediatric patients unable to swallow a capsule by opening the capsule and sprinkling the contents on food. The smallest Ultrase® capsule dose is (b) (4) units of lipase.

There are approximately 10 different sponsors and formulations for enteric-coated PEPs that currently are under IND or undergoing NDA evaluation. Thus, it is likely that pediatric drug development recommendations for Creon® will be applied to the other PEPs.

Discussion

Pancreatic Insufficiency in CF

The literature notes that poor clinical outcomes are associated with under-nutrition of CF patients, and that 85 – 90% of CF patients have pancreatic insufficiency associated with under-nutrition. When the diagnosis of CF has been established, pancreatic insufficiency is often inferred by clinical signs and symptoms such as frequent, malodorous, greasy stools, the presence of meconium ileus, or distal intestinal obstruction syndrome. Consequently, when pancreatic insufficiency is present, pancreatic enzyme therapy should be started (Borowitz *et al.*, 2002).

Fibrosing Colonopathy

According to Borowitz, et. al., the term fibrosing colonopathy describes a condition associated with ingestion of large quantities of pancreatic enzyme supplements. The authors report that fibrosing colonopathy can lead to colonic strictures and should be considered in CF patients who have evidence of obstruction, bloody diarrhea, or chylous ascites, as well as in patients who have a combination of abdominal pain with continuing diarrhea, poor weight gain, or both. Patients at highest risk include those who are < 12 years old, have taken more than 6000 lipase units/kg per meal for more than 6 months, have a history of meconium ileus or distal intestinal obstruction syndrome, have had any intestinal surgery, or have a diagnosis

of inflammatory bowel disease. The definitive diagnosis can be made only by microscopic evaluation of surgical resection specimens (Borowitz *et al.*, 1995).

Pediatric Dosing Recommendations for PEPs

In March 1995, the US Cystic Fibrosis Foundation (Foundation) organized a Consensus Conference on Enzyme Therapy and Fibrosing Colonopathy that examined the use of pancreatic enzymes in CF patients. The resulting 1995 Consensus Report notes that there is great inter-individual variation in response to enzymes, and thus a range of doses is recommended. The report recommends the following enzyme dosing for children:

- Standard meal dosing
  - Infants - 2000 to 4000 lipase units per 120 ml of formula or per breast-feeding
  - Children < 4 years old – starting dose of 1000 lipase units/kg per meal
  - Children > 4 years old – starting dose of 500 lipase units/kg per meal (older children tend to ingest less fat per kilogram of body weight)
- Snack dosing - ½ the standard dose
- Total daily dose - should reflect approximately three meals and two or three snacks per day (Borowitz *et al.*, 1995).

The 1995 Consensus Report also states that it is unknown whether doses between 2500 and 6000 lipase units/kg per meal are safe. Therefore, the report recommends cautious use of PEP doses greater than 2500 lipase units/kg per meal only if they are documented to be effective by 3-day fecal fat measurements that indicate a significantly improved coefficient of absorption. As noted in the prior section above, PEP doses greater than 6000 lipase units/kg per meal have been associated with colonic strictures in children < 12 years old, regardless of whether standard-strength or high-strength pancreatic enzymes were taken (Borowitz *et al.*, 1995). A subsequent article examining PEPs and fibrosing colonopathy in children with CF recommends a PEP dosing limit of 10,000 lipase units/kg per day (FitzSimmons *et al.*, 1997).

In 2001, the Foundation and the North American Society for Pediatric Gastroenterology sponsored a Consensus Conference on Nutrition for Pediatric Patients with Cystic Fibrosis. The resulting 2002 Consensus Conference Report reaffirmed that PEP doses should be less than 2,500 lipase units/kg per meal or less than 4000 lipase units/gram of fat per day to avoid fibrosing colonopathy. The authors refer readers to the 1995 Consensus Conference Report for a more complete discussion of pancreatic enzyme replacement therapy (Borowitz *et al.*, 2002).

Pediatric Dosing Consideration for Creon®

The Division reports that children as young as 1 month old currently use PEPs. Thus, the pediatric population for which studies will ultimately be needed includes children 1 month to 16 years old. In its consultation request, the Division has expressed concern that the administration of Creon® capsules (6000 lipase units) in young, small children would result in inaccurate dosing and the potential for both under- and over-dosing (by lipase units), both of which carry potentially serious health risks for children. The Division is especially concerned about the potential to overdose and the risks of fibrosing colonopathy.

For infants, the 1995 Consensus Report recommends PEP dosing of 2000 to 4000 lipase units

per 120 ml of formula or per breast-feeding. Therefore, if Creon® capsules (6000 lipase units) were used in this population, the parent and/or caregiver would have to approximate the 1/3 to 2/3 of the capsule contents to achieve the recommended dose. Such an approximation likely would be difficult to do. Of note, if a 1 month old girl weighing 4 kg (50th percentile weight for age) were given the entire 6000 lipase units, this would equate to 1,500 lipase units/kg which is less than the generally recommended maximum dose of 2,500 lipase units/kg per meal. However, 6000 lipase units per meal for an infant eating 8 – 12 times a day would result in 48,000 – 72,000 lipase units per day (12,000 – 18,000 lipase units/kg per day for a 4 kg infant). This would exceed the current recommendation of 10,000 lipase units/kg per day.

The following chart provides PEP dosing calculations for girls, 1 to 10 years old (based on 50th percentile weight for age), according to the current weight-based dosing recommendations in the literature (since girls typically weigh less than boys of the same age, girls' weights were used to estimate a minimum lipase dose by age). As would be expected, the calculated lipase doses infrequently corresponded to that of 1 or more full Creon capsules (6000 lipase units). For most ages, the starting meal dose equated to lipase units that exceed that of a Creon capsule by some fraction of a capsule dose. It is unclear to this reviewer if a clinically meaningful effect would be seen if the calculated fraction of a capsule were not included in the administered dose. However, for multiple ages, the starting snack dose is a fraction of 1 Creon capsule, and making such approximations would be difficult for parents and/or caregivers.

Age (yrs)	Weight (kg)	Weight Based Dosing Recommendation	Recommended Starting Dose per Meal		Recommended Starting Dose per Snack (½ meal dose)	
			Lipase Units	Number of Creon Capsules	Lipase Units	Number of Creon Capsules
1	9.5	1000 lipase units/kg per meal	9,500	~ 1 ½	4,750	¾
2	12	"	12,000	2	6,000	1
3	14	"	14,000	~ 2 ⅓	7,000	> 1
4	16	500 lipase units/kg per meal	8,000	~ 1 ⅓	4,000	⅔
5	18	"	9,000	1 ½	4,500	¾
6	20	"	10,000	1 ⅔	5,000	< 1
7	23	"	11,500	< 2	5,750	~ 1
8	26	"	13,000	> 2	6,500	> 1
9	29	"	14,500	~ 2 ½	7,250	~ 1 ¼
10	33	"	16,500	~ 2 ¾	8,250	~ 1 ⅓

Pediatric Research Equity Act

PREA (21 USC 355c) requires sponsors to submit pediatric assessments when they submit an application or supplemental application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Per 21 USC 355c(a)(2)(A),

> The assessment shall contain data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate —
>
> i) to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and
> ii) to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective.

Per 21 USC 355c(a)(3), the Secretary may defer submission of some or all assessments required until a specified date after approval of the drug if the drug is ready for approval in adults before pediatric studies are complete AND the applicant submits:

i) certification of the grounds for deferring the assessments;
ii) a description of the planned or ongoing studies; and
iii) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

When a Division agrees to defer the submission of all or part of the pediatric assessment, the deferred pediatric studies become required postmarketing commitments at the time of the approval action.

Responses to the Division's Questions

1) [Pediatric Research Equity Act] PREA regulations state that age-appropriate formulations must be developed and tested in the pediatric population for products that will be used in children. Do you feel that the current practice of breaking open capsules, approximating the dose, and administering PEPs sprinkled on food is adequate and consistent with PREA and that the PEPs may be safely administered in this manner?

PMHS Response: In general, sprinkling the entire contents of an open PEP capsule and administering it in food could be adequate for pediatric populations if dosing, safety, and effectiveness are documented in pediatric populations using this administration method and if the capsule contains the appropriate pediatric dose. However, instructing parents and other caregivers to approximate a portion of capsule sprinkles to be administered is not adequate. Partial administration of capsule contents is likely to result in under- and/or over-dosing (by lipase units), and both of these cases pose potential health risks for pediatric patients.

Of note, if the Sponsor chooses to study the open PEP capsule in pediatric populations, it will be important for it to assess if the enteric-coated spheres cause oral mucosa and/or other gastrointestinal irritation or ulceration.

2) If the response to number 1 is no, do pediatric formulations for PEPs need to be developed, and should this be a condition of approval for all PEPs intended for use in children? Do you have any specific recommendations for the development of these pediatric formulations?

PMHS Response: Since PEPs are used by the pediatric population down to 1 month old, PEP sponsors must submit a pediatric assessment containing data gathered using appropriate formulations for pediatric patients 1 month to 16 years old.

The currently recommended pediatric PEP dosing in the literature is:

- ***Standard meal dosing***
  - ***Infants - 2000 to 4000 lipase units per 120 ml of formula or per breast-feeding***
  - ***Children < 4 years old – starting dose of 1000 lipase units/kg per meal***
  - ***Children > 4 years old – starting dose of 500 lipase units/kg per meal (older children tend to ingest less fat per kilogram of body weight)***
- ***Snack dosing - ½ the standard dosing***
- ***Total daily dose - should reflect approximately three meals and two or three snacks per day (Borowitz et al., 1995). A PEP dosing limit of 10,000 lipase units/kg per day also has been recommended (FitzSimmons et al., 1997).***

Consequently, it appears that PEP sponsors will need to develop one or more lower dose capsules or a different formulation type (e.g., liquid suspension) to adequately confirm currently recommended dosing for pediatric populations. Although formulations allowing for smaller dosing units are particularly important for young children, smaller dosing units also may be useful to better approximate the minimally needed dose in older children and adults.

In the case of Creon®, pediatric studies and supporting literature may establish that the current 6000 lipase unit capsule is safe and effective for all pediatric subpopulations (i.e., that the current recommendation of 10,000 lipase units/kg per day is an underestimation of the safe, daily dose). However, I doubt this will be the case for other PEP products that have higher capsule doses (e.g., Ultrase® capsule with (b) (4) units of lipase).

Please note that if a PEP is ready for approval in adults before pediatric studies are complete, it is acceptable for the Division to defer submission of some or all of the pediatric assessments required under PREA and to make the deferred pediatric studies required postmarketing commitments at the time of the approval action.

3) Do you have any additional comments or recommendations?

PMHS Response: Please note that per PREA of 2007, the Pediatric Review Committee (PeRC) must review all decisions regarding PREA waivers, deferrals, and pediatric plans and assessments prior to the Division taking

approval action. The Division is encouraged to discuss pediatric drug development issues with sponsors. However, in order to allow for consideration of issues raised by the PeRC, the Division should not make any final agreements with sponsors until after the PeRC's review.

Reference List

Borowitz,D., Baker,R.D., and Stallings,V. (2002). Consensus report on nutrition for pediatric patients with cystic fibrosis. J Pediatr. Gastroenterol Nutr. *35*, 246-259.

Borowitz,D.S., Grand,R.J., and Durie,P.R. (1995). Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. J Pediatr. *127*, 681-684.

FitzSimmons,S.C., Burkhart,G.A., Borowitz,D., Grand,R.J., Hammerstrom,T., Durie,P.R., Lloyd-Still,J.D., and Lowenfels,A.B. (1997). High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. N Engl J Med *336*, 1283-1289.

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CLINICAL REVIEW

Application Type	NDA
Submission Number	20-725
Submission Code	AZ
Letter Date	17 November, 2006
Stamp Date	20 November, 2006
Original PDUFA Goal Date	20 May, 2007
Extended PDUFA Goal Date	18 August, 2007
Reviewer Name	Ethan D. Hausman, MD HFD-180
Through	Anne R. Pariser, MD Clinical Team Leader
Review Completion Date	16 August, 2007
Established Name	Pancrelipase Delayed-Release Capsules, USP
(Proposed) Trade Name	Creon® 6, 12, 24 capsules Minimicrospheres®
Therapeutic Class	Pancreatic Enzyme Product
Applicant	Solvay Pharmaceuticals, Inc
Priority Designation	Priority Review
Formulation	For oral administration
Dosing Regimen	Not to exceed 6,000 USP lipase units/kg/meal
Indication	Pancreatic insufficiency and steatorrhea
Intended Population	Patients with exocrine pancreatic insufficiency

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Abbreviations

The following non-standard abbreviations are used throughout this review:

CMP	Currently marketed product
TbMP	To-be-marketed product
MMS	Creon Minimicrospheres
MS	Creon Microspheres
PEP	Pancreatic Enzyme Product
PEI	Pancreatic exocrine insufficiency
CF	Cystic Fibrosis
CP	Chronic Pancreatitis
PY	Pancreatectomy
AP	Acute Pancreatitis
MedDRA	Medical Dictionary for Regulatory Activities
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
SOC	System Organ Class
PT	Preferred Term
ITT	Intent to treat population
PP	Per protocol population
R	Randomized
DB	Double blind
SB	Single blind
OL	Open label
PC	Placebo controlled
RW	Randomized withdrawal
CO	Cross over

EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This Reviewer recommends an Approvable (AE) action.

The safety and efficacy of the Creon MMS (CMP) have been established for the treatment of steatorrhea in patients with PEI, ages one month to adult. However, except for one bridging study, no clinical trials have been performed with the Creon to-be-marketed product (TbMP). The bridging study failed to establish the clinical comparability of the CMP and TbMP. Therefore, data in this CR are not adequate to support the approval of Creon TbMP.

One or more short term, efficacy and safety clinical trials with Creon TbMP are required to establish the safety and efficacy of the Creon TbMP. These studies are to be performed in patients with pancreatic exocrine insufficiency, such as cystic fibrosis. Efficacy in these clinical trials is to be demonstrated by a change in coefficient of stool fat absorption (CFA) from non-treatment or placebo treatment compared to CFA during treatment with the TbMP.

1.2 Recommendation on Postmarketing Actions

No post-marketing actions are warranted at this time.

1.2.1 Risk Management Activity

No risk management activities are warranted at this time.

1.2.2 Required Phase 4 Commitments

No phase 4 commitments are warranted at this time.

1.2.3 Other Phase 4 Requests

No other Phase 4 requests are warranted at this time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

1.3.1.1 Regulatory Background of Pancreatic Enzyme Products

Pancreatic Enzyme Products (PEPs) were first marketed prior to the Food Drug and Cosmetic Act of 1938 and continue to be available in the US as nutritional supplements and throughout the world as over-the-counter (OTC) and prescription therapies. In the 1990's concerns about potency and safety, including fibrosing colonopathy, led to a series of regulatory decisions establishing that PEPs were not generally recognized as safe and effective. It was determined that PEPs would be considered misbranded due to variations in potency. The Agency then declared its intent to consider all PEPs as new drugs requiring an approved new drug application (NDA) for continued marketing. This position was reaffirmed on 25 April 1995 with the publication of a Final Rule calling for all PEPs to be marketed drug products under approved NDAs by April 2008.

There is no currently available delayed release PEP approved for marketing in the US, though Creon and other PEPs are currently available as OTC nutritional supplements or prescription medicines in multiple other countries. The only previously approved PEP (Cotazym, approval December 1996) is not currently marketed in the US.

1.3.1.2 Overview of Clinical Program

Creon Pancrelipase Delayed-Release Capsules are classified as PEPs. PEPs contain a combination of lipases, amylases, and proteases, and are orally administered to patients with steatorrhea due to pancreatic enzyme insufficiency dues to a variety of primary disease processes, such as cystic fibrosis (CF).

In this Complete Response to a Not Approved action, the Sponsor submitted a request for approval of Creon® Minimicrospheres® (Creon MMS) for the indication for treatment of steatorrhea due to pancreatic exocrine insufficiency (PEI) associated with cystic fibrosis (CF) and chronic pancreatitis (CP). In support of this request, the Sponsor submits data from two new clinical trials of the CMP, an updated integrated summary of safety (ISS), including safety data from approximately 50 studies, 12 of which were not included in the original ISS, and data from a new bridging study conducted for the purpose of attempting to demonstrate the clinical comparability of Creon CMP with Creon TbMP.

This document reviews one new study of the CMP in adult patients with CP and PY (e.g., the New Adult PEI Study) and one new study in infants with CF (e.g., the New Infant CF Study), and the updated ISS, and contains summaries of clinical studies performed in CF and CP patients reviewed in the original NDA regulatory cycle (i.e., the Prior Pediatric CF, Prior Adult CF, and Prior Adult PEI studies). Selected information from other clinical studies is presented where noted.

Summary comments from other review disciplines are presented, including the Clinical Pharmacology review of the Bridging study (S245.2003), the Toxicology evaluation of the o-phthalic acid toxicology evaluation (study S0010.7.637X) and animal toxicology studies submitted under the Creon IND 47,546, the Division of Scientific Investigation (DSI) inspection report, the Chemistry, Manufacturing and Controls review, the Virology review, and the Microbiology review.

1.3.2 Efficacy

Two new short-term clinical efficacy and safety trials of Creon MMS (CMP) in patients with PEI were submitted in this CR amendment to the NDA and were reviewed for efficacy. Three short-term clinical efficacy and safety trials of Creon MMS (CMP) were submitted in the original NDA, and have been previously reviewed and summarized for efficacy during the original NDA review cycle. These five studies collectively enrolled 86 patients with CF, ranging in age from one month to 53 years, and 121 adult patients with PEI due to chronic pancreatitis (CP; n=62), and pancreatectomy (PY, n=59). The primary efficacy measure in these studies was coefficient of stool fat absorption (CFA) from non-treatment or placebo treatment compared with CFA during treatment with Creon MMS (CMP).

Efficacy results from studies are summarized below.

- New Infant CF Study (S248.3.003): In this short term, open-label study of 12 infants with CF, between one and 24 months of age, mean increase in CFA with Creon treatment compared to a no-treatment Baseline was 27% (95% C.I. 12.3, 41.1). Increase in CFA was greatest in four patients with non-treatment CFA less than 40%. Statistical inferences could not be made due to the small size of the study; however the clinical findings showed a clinically meaningful benefit of Creon treatment, and the magnitude of the results are similar to results seen in older pediatric and adult patients with CF. Thus, this study supports the clinical effectiveness of Creon CMP treatment of infants with PEI due to CF as young as one month of age.

- New Adult PEI Study (S245.3.115): In this short term, double-blind, placebo-controlled trial of low-dose and high-dose Creon MMS (CMP) in patients with PEI due to CP (N=35) and PY (N=59), mean increase in CFA for the ITT population (CP and PY) was 12% in patients receiving high-dose Creon MMS (CMP) compared to placebo (p-value 0.015). In the pancreatectomy sub-population, increase in CFA was approximately 18% in the high-dose Creon group compared to placebo (p-value 0.011). No significant difference in mean CFA compared to placebo was demonstrated in the low-dose Creon group (overall or by sub-population), or in CP patients treated with either low-dose or high-dose Creon CMP.

  The Sponsor performed an unplanned interim analysis during the study, and the potential effects on measure of statistical success were not provided. Therefore, no statistical inferences can be made for this study, and this Reviewer concludes that the results of the Adult PEI Study can not be used to support the efficacy of Creon CMP treatment for PEI due to CP or PY.

- Prior Pediatric CF Study (S223.3.101): In this short term, randomized, double-blind, placebo-controlled, treatment withdrawal trial of 38 children with CF, aged 7 through 17 years, CFA

was 31% higher (p-value < 0.001) in the Creon MMS (CMP) treatment group (N=18) compared to the placebo group (N=20). These findings show a statistically significant and clinically meaningful benefit of Creon treatment in pediatric patients with PEI due to CF, ages seven years and older.

- Prior Adult CF Study (S223.2.102): In this short term, randomized, double-blind, placebo-controlled, treatment withdrawal trial of 36 adults with CF, ages 18 through 53 years, CFA was 35% higher (p-value < 0.001) in the Creon MMS (CMP) treatment group (N=18) compared to the placebo group (N=18). These findings show a statistically significant and clinically meaningful benefit of Creon treatment in adult patients with PEI due to CF, ages eighteen and older.

- Prior Adult PEI Study (S223.2.01): In this short term, randomized, double-blind, placebo-controlled, treatment trial of 27 adults with CP, ages 38 through 74 years, CFA was 16% higher (p-value 0.0185) in the Creon MMS (CMP) treatment group (N=12) than the placebo group (N=14). These findings show a clinically meaningful benefit of Creon treatment in adult patients with PEI due to CP.

In conclusion, it is the overall assessment of this Reviewer that data from three short-term clinical efficacy and safety studies conducted in pediatric and adult patients with CF, and adult patients with CP support the effectiveness of Creon CMP treatment of steatorrhea in patients with PEI, and that Creon's effectiveness appears to be greatest in the most severely affected patients (i.e., patients with the lowest Baseline CFA). Results from the New Infant CF study were supportive of the clinical effectiveness of Creon CMP in the treatment of steatorrhea in infants with CF, ages one to 24 months these patients, and the results from this study were consistent with the results seen in clinical studies in older pediatric and adult patients. These findings support the labeling of Creon CMP for the treatment of steatorrhea in patients with PEI, ages one month to adult. The results from the New Adult PEI study cannot be used to support the effectiveness of Creon CMP in the treatment of PEI, due to problems with study conduct, and because of the results of the study were not clinically meaningful.

The Sponsor intends to market the Creon TbMP. However, no efficacy and safety clinical trials have been conducted to date with the Creon TbMP. The Bridging study that was submitted to the CR amendment, and was conducted for the purpose of demonstrating the comparability of the Creon CMP and TbMP products, failed to demonstrate the clinical comparability of the two products. Thus, the efficacy and safety results from studies with the Creon CMP cannot be used to support the clinical efficacy and safety of the Creon TbMP. Therefore, the efficacy (and safety) of the Creon TbMP for the treatment of steatorrhea in patients with PEI has not been demonstrated, and the information submitted in this CR amendment does not support the approval of Creon TbMP.

1.3.3 Safety

The Safety Update in this CR amendment contains information from 57 clinical studies conducted between July 1985 and May 2006, and performed with Creon MMS (CMP) or other formulations that are no longer marketed (e.g., Creon MS). Of the 57 studies in the ISS, 52 are multiple-dose studies

and five are single-dose studies. Safety information from 12 of the 57 studies is submitted for the first time in this CR amendment. Seven studies were not incorporated into the ISS due to data quality issues (e.g., inadequate methods for data collection, and incomplete safety datasets), and were not included in this safety review. Therefore, the ISS contains safety information from 50 studies.

Studies reported in the ISS include open-label, single- and double-blind, placebo-controlled, and uncontrolled trials, and contains information on 1,546 patients. Of 1,546 patients, 743 had CF, 358 had CP, 153 had pancreatic surgery, 109 had diabetes mellitus, 77 had acute pancreatitis, and 106 had other processes. Of 1,333 patients exposed to any Creon product, 991 received Creon MS (116 under double-blind conditions; Creon MS is not the CMP), and 594 received Creon MMS (232 under double blind conditions). Treatment exposure to Creon MMS ranged from six to 90 days (most common exposure was two to six weeks). Gender representation approximately 60% male and 40% female, and the age range of patients included in the Safety Update was from one month to more than 80 years of age.

The safety results are notable for the following:

Deaths

Eight death reports were included in the ISS and ten death reports were received from other sources (post-marketing and global safety surveillance reports). All deaths were attributable to underlying diseases, including recurrence/metastasis of carcinoma and pre-existing cardiovascular or cardiopulmonary disease. No deaths were attributable to Creon MMS (CMP). No pediatric deaths were reported. This Reviewer concludes that the deaths reported in the Complete Response were attributable to underlying disease and were not causally related to use of Creon MMS (CMP).

SAEs and Withdrawals

- In the ISS, SAEs were reported in 3.4% of patients receiving Creon MMS (CMP) and 3.4% of patients receiving placebo. The most common SAEs by System Organ Class (SOC) were gastrointestinal disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders. The most common SAEs by Preferred Term (PT) were pyrexia, cough, acute bronchitis, superinfection of the lung and hypoglycemia. In the opinion of this Reviewer, there was no clinically meaningful difference in incidence or type of SAEs between Creon MMS (CMP) and placebo treatment groups, and the SAEs reported were generally consistent with underlying disease.

- The most common SAEs in children with cystic fibrosis treated with Creon MMS (CMP) in the three pediatric CF safety studies included in the ISS were gastrointestinal disorders, and upper and lower respiratory tract infections. These SAEs appear to be consistent with underlying disease. An increased incidence of SAEs in children treated with Creon MMS (CMP) in these three studies was noted compared to patients treated with placebo (7% compared to 3%). The relevance of this finding is unclear, but may be explained by a greater exposure time of patients to Creon MMS (about 524 patient-weeks of exposure) than to placebo (about 60 patient-weeks of exposure).

- About 3% of patients in the ISS withdrew, including 2% of patients treated with Creon MMS and 3% in patients treated with placebo. The types of AEs leading to withdrawal were similar to the reported SAEs and commonly reported AEs, and appear to be related to underlying diseases and unrelated to administration of Creon MMS (CMP). An increased incidence of withdrawal was noted in patients with acute pancreatitis, which may be explained by the rapidly changing clinical state in patients with acute pancreatitis.

This Reviewer concludes that SAEs and withdrawals reported in the Safety Update were attributable to underlying disease, were expected in the patient populations under study, and did not appear to be causally related to use of Creon MMS (CMP).

Common Adverse Events

AEs were more common in patients treated with Creon MMS (61%) than in patients treated with placebo (49%). This disparity appears to be due to an increased incidence of less commonly reported AEs in the Creon MMS population, such as epistaxis and nasal congestion, than in patients treated with placebo. This disparity may also be due to differences in study designs for studies included in the ISS (e.g., open-label and lack of placebo control in many studies, which limited the placebo experience). However, the types and frequencies of the most commonly reported AEs in the ISS population are substantially similar between patients treated with Creon MMS (CMP) and patients treated with placebo, and include headaches, abdominal pain and other gastrointestinal complaints, respiratory disorders, and upper and lower respiratory tract infections. There were no obvious differences in the types of AEs reported by patients with different Baseline diagnoses or by age.

Special Safety Considerations with PEPs/Creon

Fibrosing colonopathy has been reported in children with Cystic Fibrosis treated with pancreatic enzyme products. No cases of fibrosing colonopathy (FC) were reported in the ISS, which is not unexpected due to the short duration of the studies and the relatively small safety population. One case of FC was reported in post-marketing reports, which was not definitively attributable to treatment with Creon MMS. Monitoring for FC is to be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products.

Hyperuricemia has been reported in patients with pancreatic exocrine insufficiency treated with PEPs. Though blood and urine uric acid monitoring were was not assessed in all studies in the ISS, hyperuricosuria was noted in several patients in the Prior Pediatric CF and Prior Adult CF Studies, all of whom had non-treatment blood uric acid levels near the upper limit of normal. Monitoring for hyperuricemia is to be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products.

In conclusion, in the opinion of this Reviewer, the safety of Creon MMS (CMP) has been adequately assessed. Withdrawals, SAEs, and non-serious AEs reflect findings reported in the original review of this NDA and in open source literature of patients with cystic fibrosis, and other causes of pancreatic exocrine insufficiency, and commonly include headaches, abdominal pain and other gastrointestinal

complaints, respiratory disorders, and upper and lower respiratory tract infections. AEs were most commonly attributable to underlying disease and appear unrelated to administration of Creon MMS (CMP). There were no new or notable safety findings with Creon administration reported in the Safety Update of the CR amendment to the NDA. In addition, all of the appropriate patient populations were studied in the Creon CMP clinical development program, including patients with cystic fibrosis as young as one month of age through adulthood, and patients with PEI due to other causes, such as CP.

Since the Bridging study failed to establish the comparability of the Creon CMP and TbMP, the safety results obtained with Creon CMP cannot be solely relied upon to demonstrate the safety of Creon TbMP, and at least one additional short-term safety (and efficacy) study with Creon TbMP will need to be performed to support the NDA approval of Creon TbMP.

1.3.4 Dosing Regimen and Administration

In order to optimize therapy while minimizing the risk of fibrosing colonopathy (FC), the Cystic Fibrosis Foundation (CFF), in conjunction with the FDA, recommends starting lipase doses according to age as described below.

The CFF recommends the following dose schedule for full meals:

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.
- Children ≤4 years old eating soft or solid foods: begin with 1,000 USP lipase units/kg/meal.
- Children >4 years old: begin with 500 lipase units/kg/meal.
- Doses in excess of 2,500 USP lipase units/kg/meal should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to significantly improve a documented low coefficient of fat absorption.
- The recommended per meal dose should be halved when ingesting snacks.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with fibrosing colonopathy.

Because safety and efficacy of the Creon TbMP have not been demonstrated in clinical trials, the final dose recommendations may change based on results of clinical trials of the TbMP; however, dosing recommendations for the TbMP should be consistent with current Cystic Fibrosis Foundation guidelines. The Sponsor's proposed dosing in the draft labeling for the CMP for pediatric patients is weight-based, and is generally consistent with the CFF guidelines.

- For adult patients with CP and pancreatectomy (PY), dosing should be individualized. The Sponsor recommends [redacted] (b) (4)

(b) (4)

This Reviewer recommends that the maximum doses in final labeling not exceed the maximum doses studied for these indications.

1.3.5 Drug-Drug Interactions

It is expected that patients with PEI may be exposed to prokinetic agents, H-blocking anti-histamines, and antacids. The efficacy studies included in the CR amendment allowed patients to be on these medicines if the dose was stable at the beginning and throughout study. In addition, many patients included in the studies in the CR amendment were on a large number and variety of medications for treatments of co-morbidities associated with underlying disease (e.g., antibiotics for infectious complications of CF). No reports of drug-drug interactions were noted in the CR amendment. Since Creon is not systemically absorbed, no interactions with systemically-active medications would be expected, although drug-drug interactions were not formally assessed as part of the Creon clinical development program.

1.3.6 Special Populations

The Creon clinical development program was conducted in patients where PEI is part of primary pathophysiology, including CF, CP, and PY, and in processes where PEI may present less commonly (e.g., diabetes mellitus). The clinical development program focused mainly on patients with CF, CP and PY.

Cystic fibrosis is an autosomal recessive disease estimated to occur in about 1 in 1,500 to 1 in 2,500 live births in the US, and affects an estimated 30,000 persons in the US. No cure exists but supportive treatment with anti-infectives, pancreatic enzyme supplements, and pulmonary, cardiac, and hepatic support has extended life expectancy out of childhood into the fourth and fifth decades. A majority of patients with CF have PEI, and CF patients account for about 42% of the population in the five key studies reviewed (New Infant CF, New Adult PEI, Prior Pediatric CF, Prior Adult CF, and Prior Adult CP Studies). The capacity to respond to treatment, demonstrated by increase in %CFA, appears to mirror severity of PEI, with more severely affected patients demonstrating greater response. This trend in response was seen in infants, youths, and adults with CF.

Studies in patients with cystic fibrosis included patients of both genders. The Sponsor provided information on children from one month of age through adulthood. The Sponsor provided safety information on children with cystic fibrosis less than seven years of age, and provided efficacy data on infants from one through 23 months of age. Adults with cystic fibrosis, from 18 to 53 years were also studied. Though the number of patients studied was small, males and females with CF appear to respond similarly. As expected, from epidemiological characteristics of cystic fibrosis, the CF population studied was predominantly Caucasian; therefore, there is insufficient information to determine any difference in response to treatment in CF patients based on ethnicity.

Pancreatectomy produces definitive and severe PEI. Pancreatectomy is a rare circumstance, offered as a component of treatment for certain gastric or pancreatic cancers, or as a result of trauma care. Patients with PY account for about 29% of the population in the five key studies. Similar to patients with CF, patients with more severe baseline disease demonstrated greater response.

In the opinion of this Reviewer, patients likely to be treated with Creon in the post-marketing setting, including the special populations noted above, have been adequately studied with Creon CMP in the Creon clinical development program.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The investigational agent studied in the application is Creon® Minimicrospheres® (MMS). Creon MMS is a delayed-release formulation of porcine-derived pancrelipase. Pancrelipase is derived from porcine pancreata, and contains varying amounts of lipases, amylases, and proteases, which break down lipids, carbohydrates, and proteins. Creon MMS was provided as gelatin capsules for oral administration. The Sponsor (Solvay) intends to market the product under the trade name Creon® 6, 12, and 24 capsules, which contain 6,000, 12,000, and 24,000 units of lipase, respectively.

Creon MMS is intended to provide an exogenous source of orally administered pancreatic enzymes to pediatric and adult patients with pancreatic exocrine insufficiency (PEI) from a variety of causes, such as Cystic Fibrosis (CF) and chronic pancreatitis (CP).

2.2 Currently Available Treatment for Indications

Pancreatic enzyme products (PEPs) have been marketed in the United States (US) without New Drug Applications (NDAs) since before the Federal Food, Drug and Cosmetic Act (The Act) of 1938. PEPs are currently widely available in the US as nutritional supplements produced and distributed by a number of manufacturers and sponsors. PEPs are available in enteric coated/delayed-release, and non-enteric coated formulations, which are not considered to be interchangeable.

One PEP (Cotazym) received NDA approval in December 1996, but is not currently marketed in the US. Thus, there is no pancreatic enzyme replacement therapy currently marketed in the US under an NDA.

2.3 Availability of Proposed Active Ingredient in the United States

Creon is currently commercially available in the US, but has not yet received approval under an NDA. Creon brand capsules first became commercially available in the US in 1987 as Creon Microsphere® (MS) capsules. In 1993, the Sponsor introduced the MMS form of Creon to replace the MS form. Currently, Creon MMS has marketing authorizations in approximately 70 countries worldwide.

Note: The Creon MMS formulation currently marketed in the US is referred to as the currently marketed product (CMP), and is a different formulation from the product formulation being proposed for NDA approval (the to-be-marketed product; TbMP).

2.4 Important Issues with Pharmacologically Related Products

PEPs were first marketed prior to The Act of 1938. Due to concerns about variability in potency, the Agency published a Notice of Proposed Rule making in the Federal Register (FR) on 15-July-1991 establishing that Over-the-Counter (OTC) PEPs are not considered generally recognized as safe and

effective (GRAS, and GRAE) products, and that OTC and prescription PEPs were considered misbranded due to variations in potency. Concurrently, the Agency declared its intention to consider all OTC and prescription PEPs to be new drugs requiring an approved NDA for continued marketing. This position was reaffirmed on 25-April-1995 with the publication of a Final Rule calling for all PEPs to be marketed drug products under approved NDAs in order to remain on the market. In April 2004, the Agency published in the FR a Notice of Requirement for NDA Approval of all PEPs within the next four years, with a deadline of 28-April-2008.

A single previously NDA approved PEP (Cotazym, approval December 1996) is not currently marketed in the US. Therefore, there is no currently available PEP approved for marketing in the US under an NDA, although Creon and other PEPs are expected to remain available as OTC products, nutritional supplements, or prescription medicines in the US until the 28-April-2008 deadline.

2.5 Presubmission Regulatory Activity

Creon is undergoing clinical investigation under Investigational New Drug Application (IND) 47,546. A summary of the regulatory history of Creon is as follows:

- Solvay Pharmaceutical Inc. (the Sponsor) originally submitted NDA 20-725 for Creon Microspheres (MS; pancrelipase delayed-release capsules) on 31-July-1997. On 24-September-1997, review of the NDA was suspended, and the Sponsor was placed on Application Integrity Policy (AIP) due to data integrity issues. The AIP was removed on 9-April-2003, and the review resumed under priority status.

- A Not Approved (NA) decision was rendered on 9-October-2003. Deficiencies noted in the NA letter from the Agency to the Sponsor included major CMC deficiencies, including a lack of drug product stability, inadequate characterization and specifications of drug substance and drug product, and incomplete viral safety evaluations. The letter additionally stated that once the CMC deficiencies were corrected, the Sponsor would need to link the intended to-be-marketed formulation (TbMP) with the formulation (CMP) used in the clinical trials. Methods to establish comparability of the CMP to TbMP were requested because the TbMP had not been investigated in Phase 3 clinical trials. Subsequent communications between the Sponsor and the Agency established that, in lieu of new clinical studies with the TbMP, comparability might be established by performance of a successful bridging study.

- The clinical reviewer (Fathia Gibril, M.D., M.H.Sc.), who performed the clinical review of the NDA at that time, concluded that clinical data supported the safety and efficacy of Creon MS; however, additional information was requested on children less than seven years old, who had not undergone evaluation in the Creon clinical development program.

The sponsor submitted a Complete Response (CR) to the Non-Approved decision on 20-November-2006, which is the subject of this review.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

CMC data have been extensively reviewed by the Product Reviewer (Wei Guo, Ph.D.), the Virology Reviewer (Ennan Guan, Ph.D.), and the Microbiology Reviewer (Anastasia Lolas, Ph.D.). Please see these reviews for more detailed information on the CMC data. Notable issues identified by these reviewers are briefly summarized as follows:

The Virology review (Ennan Guan, M.D., PhD) makes the following comments and recommendations:

- Manufacturing demonstrated effective inactivation of enveloped viruses, but not removal of viruses.
    - Therefore, it would be very useful if the firm can provide enveloped viral load by PCR-based test for their process intermediates to estimate the genomic equivalents.
- The Sponsor should set specifications for infectious PPV particles for the drug substance and final product, or set an action limit.

The CMC review (Wei Guo, Ph.D.) recommends an approvable (AE) action. The following specific review comments are provided:

- Adequate control of colipase activity must be ensured in drug substance and product.
    - We recommend that the measurement of lipase potency in release and stability testing be performed in both the absence and presence of excess exogenous (b) (4)
    - Acceptance criteria for activity under each assay condition should be established and justified.

- The olive oil used as lipase substrate has an acceptance criterion of oleic acid at (b) (4) of the total fatty acids, but testing results of nine batches have (b) (4) levels which vary from (b) (4)
    - Adjust the acceptance criteria of (b) (4) to reflect this fact to ensure that a consistent substrate is used in the lipase potency measurements.

- Dissolution testing of drug product should be performed on intact capsules.

- The acceptance criterion of the HPLC identity test used for drug substance and product are to be defined.

- The drug substance and product release test sampling plans are to be provided.

- The acceptance criterion of lipase activity for individual capsules tested was changed to (b) (4) of label claim on and after page 0151 of volume 1, submission dated March 21, 2007.

This is inconsistent with the proposed acceptance criteria of (b) (4) of label claim on pages 0118, 0127, 0131, 0134, and 0137 of the same submission.
    - Please address this inconsistency.

- Information on the manufacturer and specifications of container, closure, and seals for drug substance packaging is to be provided.

- Representative certificates of analysis of seals used in drug substance container/closure system are to be provided.

- Drug product labeling has been proposed as (b) (4)
    - Please specify the length of time excursions in temperature that are permitted.

The Microbiology review (Anastasia Lolas, Ph.D., 4-May-2007) recommends approval action. The following specific review comments were provided:

- (b) (4)
- *Salmonella* and *E.coli* limits, total aerobic microbial count, total combined yeast and mold counts, and post-approval stability protocols are acceptable.

3.2 Animal Pharmacology/Toxicology

Since extensive human experience exists with the PEPs, no non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA. Pharmacology/Toxicology studies submitted in this Complete Response (CR) submission were limited to evaluation of the excipient breakdown product, O-phthalic acid, conducted under and submitted to IND 47,546. Review of this information was conducted by the Animal Pharmacotoxicology Reviewer, David Joseph, Ph.D. (dated 8-June-2007). Please see the complete review of the non-clinical data for a detailed discussion of these findings.

In addition, a separate O-phthalic acid study report (S0010.7.637.X) was submitted in the NDA CR (volume 24 page 8,659). Notable issues identified by Pharmacology/Toxicology (per personal communications with Dr. Joseph on 14-June-2007) regarding the toxicology studies and the O-phthalic acid study report on 14-June-2007 are that "based on results of the submitted 4-week oral toxicity study of o-phthalic acid in dogs, the 2-year carcinogenicity studies of phthalic anhydride in rats and mice, and other preclinical studies of o-phthalic acid, p-phthalic acid, and phthalic anhydride, the estimated maximum dose of o-phthalic acid resulting from Creon® administration is not considered to be a safety concern."

Thus, there are no safety concerns identified with Creon from the review of the non-clinical data.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This application contains information from 57 clinical studies performed with Creon MMS, Creon MS, or both. Twelve studies are submitted for the first time in this CR submission. These 57 studies include all known studies conducted with Creon MMS. The studies were conducted between July, 1985 and May, 2006.

The clinical review of this application includes an assessment of clinical efficacy or outcomes measures from five Solvay-sponsored clinical studies. Two of these studies are reviewed for the first time in this document. Three of these studies were reviewed previously as part of the original NDA review for Creon (see Clinical Review by Dr. Gibril, dated 9-December-2003). These five efficacy studies include three short-term efficacy and safety studies of Creon in children and adults with Cystic Fibrosis (CF), and two short-term efficacy and safety studies in adults with chronic pancreatitis (CP) and pancreatectomy (PY). The remaining 52 trials could not be individually reviewed because of methodological deficiencies, including lack of controls, failure to study the CMP or TbMP, or lack of available study reports.

Note: A bridging study intended to compare lipase activity of the Creon CMP and TbMP preparations was performed in nine patients (see comments in the Clinical Pharmacology section of this review [Section 5], and the Biopharmacology review by Tien Mien Chen, Ph.D.). Except for the bridging study, all studies were performed with the Creon CMP. No clinical efficacy and safety studies have been performed to date with the Creon TbMP.

Safety information is provided from 57 studies. Twelve of these 57 studies are submitted for the first time with this CR. Of the 57 studies, datasets and study reports for seven studies were not provided due to data quality issues (not further clarified by the Sponsor). Therefore, the Integrated Summary of Safety (ISS) contains information from 50 studies. Additional safety data from European post-marketing reports of the MS and MMS products is also provided for review. A number of these 57 studies could not be individually reviewed because of methodological deficiencies, including lack of controls, failure to study the CMP or TbMP, and lack of available study reports.

4.2 Tables of Clinical Studies

The clinical studies reviewed or summarized in this Clinical Review are summarized in Table 1 below. These studies include one new trial of Creon MMS (CMP) in infants with CF and one new trial of CMP in adults with PEI due to chronic pancreatitis (CP) or pancreatectomy (PY), which are submitted for the first time in the Complete Response, and the two CF trials and one CP trial that were previously reviewed during the original submission of this NDA. Safety information from three trials of Creon MMS and Creon MS in children with CF included in the ISS is summarized; however review of these three trials for efficacy was not possible due to missing study reports and a lack of uniform

treatment (drug and placebo) across the three studies (a table of all clinical studies conducted with Creon MMS and Creon MS is located in Appendix section 10.2).

Table 1: List of Studies Individually Reviewed or Summarized in this Clinical Review

Study	Design	Patient Population
S248.3003 New Infant CF Study	Eight-week, open-label (OL), efficacy and safety study. Efficacy was evaluated by comparing a no-treatment baseline CFA to CFA on Creon treatment.	Infants with CF, 1 to 24 months old N=12
S245.3.115 New Adult PEI Study	Two-week, randomized (R), double-blind (DB), placebo-controlled (PC), parallel-group, efficacy and safety study of Creon (1.5 or 3.0 g/day) vs. placebo. Efficacy was evaluated by comparing a no-treatment baseline CFA to CFA after seven days of treatment.	Adults with CP and PY, 26 to 83 years N=94
S223.3.101 Prior Pediatric CF Study	Three- to six-week, DB, PC, randomized-withdrawal (RW), efficacy and safety study. All patients were treated with OL Creon upon enrollment (titrated to clinical effect), then randomized to DB Creon vs. placebo treatment. Efficacy was evaluated by comparing baseline CFA (on-treatment) to CFA in DB, RW period (while receiving Creon or placebo).	Children with CF, ages 7 to 17 years N= 38
S223.3.102 Prior Adult CF Study	Three- to six-week, DB, PC, RW efficacy and safety study of same design as Study S223.3.101 (Pediatric CF Study).	Adults with CF, 18 to 53 years N= 36
223.201 Prior Adult CP Study	Two-week, R, DB, PC, efficacy and safety study. Efficacy was evaluated by comparison of mean CFA of placebo and Creon treatment groups during the DB phase of the study.	Adults with CP, 38 to 74 years N= 27
S245.3118 Prior Infant CF Safety Study	Six-week, R, OL, cross-over (CO) study in infants with CF, which compared Creon MMS to Creon MS. Endpoint was caregiver preference of MMS vs. MS. All patients received open-label placebo for 1-2 weeks in order to establish Baseline CFA. All patients were randomized to receive either two weeks of Creon MMS followed by two weeks of Creon MS, or two weeks of Creon MS followed by two weeks of Creon MMS (OL treatment period). There was no placebo control group during the OL Treatment period..	Children with CF, ages 6 to 36 months N=40
S245.3105 Prior Pediatric CF Safety Study	Ten-week R, OL, CO study that compared efficacy and safety of Creon 10,000 MMS to Creon 8,000 MS. After a two-week run-in period with Creon 8,000, patients were randomized to receive either two weeks of Creon MMS followed by two weeks of Creon MS, or two weeks of Creon MS followed by two weeks of Creon MMS.	Children with CF, ages 3 to 17 years N=60 (60 patients received MS, 58 patients received MMS)
K245.5004 Prior Young Adult CF Safety Study	Six-week R, DB, CO study of efficacy of Creon MMS compared to Creon MS. After two to three weeks of placebo wash-out, patients were randomized to receive either two weeks of Creon MMS followed by two weeks of Creon MS, or two weeks of Creon MS followed by two weeks of Creon MMS. There was no non-treatment or placebo phase from which to establish Baseline CFA. There was no placebo control group during treatment with MMS or MS. The endpoint was comparison of mean CFA between MMS and MS treatment periods.	Patients with CF, ages 4 to 31 years N=34

4.3 Review Strategy

The most important new studies submitted to this application were the New Infant CF study (S248.3003) and the New Adult PEI study (S245.3.115). The comprehensive short-term efficacy and safety data submitted to the application for these two studies permitted substantive clinical review.

The New Infant CF study is an eight-week, open-label, uncontrolled, non-randomized, short-term efficacy and safety study of 12 infants, ages one to 24 months old, with PEI due to CF. The primary efficacy endpoint was the difference between the baseline (no-treatment) coefficient of fat absorption (CFA) compared to CFA after two weeks of Creon CMP treatment. Safety was assessed during eight weeks of Creon treatment. This study showed a clinically meaningful increase in CFA with treatment compared to no-treatment.

The New Adult PEI study is a 13-day, randomized, double-blind (DB), placebo-controlled, short-term efficacy and safety study of 94 adult patients with PEI due to chronic pancreatitis (N=35) or pancreatectomy (N=59). Efficacy endpoints were assessed after one to two weeks of DB treatment (with Creon or placebo) compared to the five-day baseline (placebo treatment) period. Safety data were collected from screening through completion of the eighth day of DB treatment. This study showed a trend toward increased CFA from baseline (no treatment) compared to CFA while on Creon treatment in the DB period.

Efficacy and safety analyses of the New Infant CF and New Adult PEI studies are emphasized in this review, and comprehensive reviews of these studies are summarized in the Appendix section under Individual Study Reports. Summaries of efficacy and safety studies (Prior Pediatric CF, Prior Adult CF, and Prior Adult CP studies) reviewed as part of the original NDA review for Creon (from Dr. Gibril's review) are also included in the Integrated Review of Efficacy section (section 6) of this review, as these studies demonstrated the efficacy of Creon CMP in the treatment of PEI.

As noted in section 4.1 of this review, substantive review of efficacy outcomes for the remaining 52 studies could not be performed due to methodological issues, including lack of adequate controls or lack of study of the MMS form of the drug. Therefore, no other studies are reviewed for efficacy.

Comprehensive individual safety reviews of the New Infant CF and New Adult PEI studies and a comprehensive safety review of the ISS were performed by this Reviewer. Review of the Prior Infant Safety, Prior Pediatric Safety, and Prior Young Adult CF Safety Studies was limited to an assessment of the Adverse Events (AEs) reported for these studies, which are summarized in the Integrated Review of Safety section (section 7) of this review. Lack of adequate controls in these three studies precluded substantive evaluation of efficacy.

4.4 Data Quality and Integrity

Data problems encountered with this application were noted during the review cycle that resulted in multiple information requests (IRs) being submitted to the Sponsor. These IRs included requests for the submission of incomplete data elements needed to complete the safety analysis. Responses from the Sponsor were sufficient to permit an evaluation of the safety data, with the exception of 1,198

adverse events from 12 studies that were not classified for seriousness or severity. Please see sections 7.1 and 7.1.5.2 of this review for a complete discussion of the issues concerning AE datasets ADVERSE, ADV, and EXTADV.

The Division of Scientific Investigation (DSI) performed one clinical site audit for this application, including inspection of the clinical site that conducted the bioequivalence/bridging study located in Marseilles, France. The overall observations noted by the DSI Inspector (Michael F. Skelly, Ph.D.) were that "The inspection could not confirm the identity of the pancrelipase products dosed to patients on each occasion. The analytical method validations and quality control programs failed to demonstrate the performance of the analytical methods before and during the study. All of the normalized study endpoints are compromised by the lack of raw data for the PEG 4000 method validation, calibration, and quality control." Thus, the overall conclusion from this inspection is that this study was not reliable as performed, and cannot be used to provide evidence of bioequivalence between the Creon CMP and TbMP.

4.5 Compliance with Good Clinical Practices

The Sponsor states that the Infant CF study and the Adult PEI study were carried out in accordance with Good Clinical Practice (GCP) regulations. The three studies reviewed during the original submission of this NDA were also reported to have been performed according to GCP regulations.

Formal assessment of GCP adherence in the older studies could not be performed. However, most of the remaining older studies submitted for review were not essential to the evaluation of the efficacy and safety of Creon. These older studies were not reviewed for efficacy, and safety information from these older studies was reviewed only as supportive evidence as part of the review of the ISS. These older studies could not be individually reviewed because of methodological deficiencies, including lack of controls, failure to study the CMP or TbMP, and lack of available study reports.

4.6 Financial Disclosures

Financial disclosure forms were reviewed for the New Infant CF study (S248.3.003), the New Adult PEI study (S245.3.115), and the Bridging study (S245.2.003). No financial interests were disclosed by any of the Investigators who participated in these studies.

Since the three efficacy studies previously reviewed in the original NDA submission (Prior Pediatric CF Study, Prior Adult CF Study, and Prior Adult CP Studies) were completed prior to 2-February-1999, disclosure of financial interest was not required. (The Agency published the Final Rule on Financial Disclosures by Clinical Investigators in the Federal Register on 31-December-1998 (21 CFR Part 54, Docket No. 93N-0445). As of 2-February-1999, compliance with disclosure of information regarding significant payments was made that applies to studies pertaining to a drug submitted for a marketing application where the study in question 1) shows that a product is effective; 2) shows equivalence to an effective product; 3) or makes a significant contribution to evidence of safety for studies ongoing as of 2-February-1999.)

5 CLINICAL PHARMACOLOGY

The clinical pharmacology data in this submission includes information from a single bioequivalence/bridging (Bridging) study (S245.2.003), titled "Cross-over pharmacology study to compare the duodenal lipase activity of two Creon® formulations in duodenal aspirates in patients with pancreatic exocrine insufficiency due to chronic pancreatitis." These data have been extensively reviewed by the Clinical Pharmacology Reviewer (Tien-Mien Chen, Ph.D.); please see the Clinical Pharmacology Review for the complete review of these data. The Bridging study was conducted for the purpose of demonstrating the comparability of the CMP and the TbMP, as all clinical efficacy studies were conducted with the CMP, and no clinical efficacy (and safety) studies to date have been conducted with the TbMP.

The Bridging study was a double-blind, randomized, single-center, 2X2 crossover, duodenal intubation study conducted in 15 adult patients with chronic pancreatitis. Each patient underwent an overnight fast, then received a meal with a dose of Creon CMP or TbMP (containing 60,000 units of lipase), and then underwent continuous duodenal aspiration collections over a three-hour period. Overall pancreatic lipase activity was determined from the aspiration specimens. Nine patients completed both phases of the study. Dr. Chen's findings for the Bridging study are briefly summarized as follows:

- The results showed that there was high inter-subject variability observed for both formulations.
    - Ten results showed that the individual values were higher than the administered dose of 60,000 units of lipase (almost four-fold the administered dose).
    - Conversely, two patients had no or little lipase activity measured in their duodenal aspiration samples.
- These observations rendered the study unreliable as a tool to establish comparability between the two formulations.
- The overall conclusion of the Clinical Pharmacology Reviewer from the data submitted in this study is that the Sponsor has not demonstrated that the TbMP is comparable to the CMP.

Thus, the comparability of the CMP with the TbMP could not be established by the Bridging study.

5.1 Pharmacokinetics

PEPs act locally in the gastrointestinal (GI) tract and are not absorbed; therefore, pharmacokinetic studies are not applicable.

Pharmacokinetic and pharmacotoxicology studies of the excipient breakdown product O-phthalic acid present in Creon tablets were performed in animal models and submitted for review under IND 47,546, and a separate pharmacokinetic summary as study report S0010.7.637.X was submitted to the NDA CR (volume 24 page 8,659). This information has been extensively reviewed by the

Pharmacotoxicology Reviewer (David Joseph, Ph.D.). Dr. Joseph's conclusions are summarized as follows:

There is no substantial risk from chronic phthalate exposures at expected daily doses of Creon, and the estimated maximum dose of O-phthalic acid resulting from Creon administration is not considered to be a safety concern.

5.2 Pharmacodynamics

Lipase, amylase, and protease act locally in the GI tract and are not systemically absorbed; therefore, pharmacodynamic studies are not applicable.

5.3 Exposure-Response Relationships

Traditionally, individual patient dosages of PEPs are determined by titration of the dose to clinical response (i.e., decreased steatorrhea/diarrhea). No formal dose-response studies were performed in support of the Creon clinical development program; however, two dosing groups were compared to placebo and against each other in the new Adult PEI Study. Please refer to the clinical review of the new Adult PEI study in Appendix section 10.1.2.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Sponsor is proposing that Creon MMS (TbMP) receive the following indication:

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

The data submitted to the Creon application is not supportive of this indication, as no efficacy studies have been conducted with the TbMP, and the Bridging study failed to establish comparability between the CMP and the TbMP. Therefore, no evidence of clinical efficacy currently exists for the Creon TbMP.

6.1.1 Methods

This Complete Response submission includes clinical efficacy measures from five short-term efficacy and safety clinical trials, two of which are newly submitted for review (Infant CF study and Adult PEI study). Supplemental efficacy information was available for review from 52 additional studies; however, the predominantly open-label and uncontrolled nature of these studies did not permit substantive review of efficacy data. Therefore, these 52 studies were not analyzed for efficacy by this Reviewer for this clinical review.

The clinical development program focused on the treatment of patients with PEI due to CF, CP, and PY. The comprehensive efficacy and safety data from the New Infant CF study and the New Adult PEI study permitted substantive review in 12 infants with CF and 94 adults with PEI due to CP (N=35) and PY (N=59), respectively. The data submitted from these studies were analyzed for the purpose of making a determination of the short-term effectiveness and safety of Creon in these patient populations. Primary and secondary efficacy endpoints and safety findings for these two trials are presented (secondary efficacy endpoints are presented only where noted). Secondary endpoints which are components of primary endpoints are not reviewed independently. The FDA Statistical Reviewer, Sonia Castillo, Ph.D., also reviewed these two efficacy studies, and conducted analyses on the primary efficacy endpoints. The findings from Dr. Castillo's review are summarized in this review.

In addition, the results for the three studies that were reviewed for safety and efficacy as part of the original NDA review for Creon were summarized (from Dr. Gibril's review) in this clinical review; however, since these studies were previously reviewed in detail, this Reviewer did not repeat the review of these studies. Instead, summaries of primary efficacy endpoints and safety findings for these three efficacy trials are presented as these studies were assessed by Dr. Gibril as having demonstrated the efficacy of Creon CMP in the treatment of PEI. Please refer to the clinical review from the original submission (Dr. Fathia Gibril, 9 December 2003) for a full discussion of the three previously reviewed efficacy trials.

Note: All of the clinical studies included in this review (with the exception of the Bridging study discussed above in section 5 Clinical Pharmacology) were conducted with the Creon CMP product. No clinical efficacy and safety studies have been performed to date with the Creon TbMP.

6.1.2 General Discussion of Endpoints

Pancreatic exocrine insufficiency (PEI) is a feature of multiple diseases, including CF and loss of functional exocrine mass (e.g., due to pancreatectomy or chronic pancreatitis). Clinical features of PEI are fat, protein, and carbohydrate malabsorption and malnutrition, and primary laboratory features include decreased blood fat soluble vitamins, increased stool fat content, and decreased CFA.

As described in published consensus documents (e.g., Borowitz, DS, Grand, RJ; Durie, PR., J Pediatrics, Nov 1995),[1] decreased CFA is an accepted indicator of PEI, and an increase in CFA is associated with enhanced pediatric growth and development.[2] A clinically meaningful increase in CFA in CF patients is accepted to be an increase of 30% or greater in the most severely affected patients (i.e., those patients who have baseline CFA less than 40%). There is no accepted clinically meaningful increase in CFA that has been determined for patients with PEI due to causes other than CF; however, as PEI due to any cause has similar clinical findings, it would be reasonable to consider this degree of change as meaningful in PEI due to PY and CP. In addition, there is no accepted change in CFA that has been shown to be clinically meaningful in patients with a Baseline CFA greater than 40%. Patients with higher CFAs at Baseline tend to have smaller increases in CFA with PEP administration, as these patients have a lesser capacity to respond. Therefore, and in concert with the Agency's "Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products –Submitting NDAs",[3] the Division accepts the use of CFA as the primary efficacy measure in the clinical studies conducted in the Creon clinical development program as reasonable and appropriate. Since it is

expected that the magnitude of change in patients' CFA with PEP administration would depend upon the Baseline (no treatment) CFA, the Division would expect to see larger increases in percent CFA (approaching 30%) in patients with the lowest Baseline CFAs (e.g., <40%), and lesser increases in CFA in patients with higher baseline CFA (e.g., >40% to <80 %).

In the five clinical studies reviewed for efficacy as part of this Clinical Review, CFA was assessed in the following manner:

Meals with pre-specified fat composition were provided, and prepared diets were consumed for five days. After completion of the second day of prepared meals, all stools produced over a 72-hour period (days three through five of prepared meal consumption) were collected. The percent CFA (%CFA) was determined using the following formula:

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

Change in CFA was measured in one or both of two ways: 1) mean change between non-treatment and treatment period; and/or 2) comparison of mean change between placebo and treatment groups compared to each group's non-treatment baseline.

In the New Infant CF study, patients were eligible for enrollment in the study if they had a Baseline CFA less than or equal to 70%, and successful treatment was defined as a treatment period CFA 90% or greater. Secondary outcome measures in the Infant CF study included change in number of stools per day, weight for height, and change in body mass index. These secondary endpoints are reviewed; however, they are of lesser importance given the short-term nature of this study, and were not felt to be substantively important to the determination of efficacy. Presentation and discussion of these secondary endpoints is found in Appendix 10.1.1 of this review.

In the New Adult PEI study, patients were eligible for enrollment in the study if the had a Baseline CFA no greater than 80%. Primary efficacy outcome was change of %CFA during the placebo period compared with change in %CFA during treatment. A definition for success for change in %CFA in this study was not provided. Secondary endpoints for this study included change in number of stools per day and change in daily caloric intake. These secondary endpoints are reviewed; however, they are of lesser importance given the short-term nature of this study, and were not felt to be substantively important to the determination of efficacy. Presentation and discussion of these secondary endpoints is found in Appendix 10.1.2 of this review.

The Sponsor also collected information on treatment-associated changes in daily dietary fat intake, and stool fat content. Dietary fat intake and stool fat content are both components of %CFA and are not independently reviewed.

6.1.3 Study Design

The two new clinical studies submitted to this application are reviewed in detail by this Reviewer: the New Infant CF study and the New Adult PEI study. The reader is directed to the individual study reports located in appendices 10.1.1 and 10.1.2, respectively, for a more detailed discussion of these studies. Additionally, summary information on the three previously reviewed trials (i.e., the Prior Pediatric CF, Prior Adult CF, and Prior Adult CP studies) is presented. New and independent reviews of these prior studies were not performed by this Reviewer.

6.1.3.1 New Infant CF Study (Study S248.3003)

6.1.3.1.1 Design, Treatment, and Population

The New Infant CF study was an eight-week, open-label, single-arm, efficacy and safety study of twelve infants with CF, age one through 24 months. Twelve infants (5 male [M], 7 female [F]) were enrolled, including five treatment naïve children, and seven children with previous exposure to PEPs (the duration of prior exposure to PEPs was three weeks to 21 months). All children underwent a no-treatment period of seven to ten days (minimum six days), which served as a wash-out period for children with prior exposure. Baseline CFA was performed after at least 72 hours of no-treatment. All children were then treated with Creon MMS for eight weeks. The daily dose was 2,000 lipase units per gram of fat intake. The study report did not indicate a maximum allowable daily dose.

6.1.3.1.2 Objectives and Outcomes Measures

The primary objectives of the study were the evaluation of efficacy after two weeks of treatment with Creon, and the evaluation of safety after two, five, and eight weeks of treatment. Efficacy was evaluated by changes from Baseline after two weeks of treatment in CFA, stool characteristics, growth indices, and laboratory evaluation of nutritional parameters. Safety was evaluated by changes from Baseline in medical history, physical examinations, and safety laboratory analyses (e.g., chemistry panel and hematology), and the occurrence during treatment of adverse events.

6.1.3.1.3 Patient Eligibility/Inclusion and Exclusion Criteria

Patients were eligible for study participation if they were ages one through 24 months, and had:

- A diagnosis of CF by two sweat tests or by gene analysis;
- PEI defined by age-adjusted steatorrhea with age-adjusted criteria, including:
    - <4 months of age: >4 g fecal fat/24 hr,
    - 4 to 12 months: >3 g/24 hr,
    - >12 months: >3-4 g/24 hr,
    - or stool chymotrypsin <5 U/g stool; and
- Baseline CFA <70% at end of no-treatment wash-out period.

Children were excluded from study participation for any known illness judged to put them at risk for participation in the study, including meconium ileus or pre-existing pulmonary disease, or known

allergy to porcine pancreatic products, or any other concomitant PEP exposure during the washout period.

6.1.3.1.4 Concomitant and Prohibited Medications

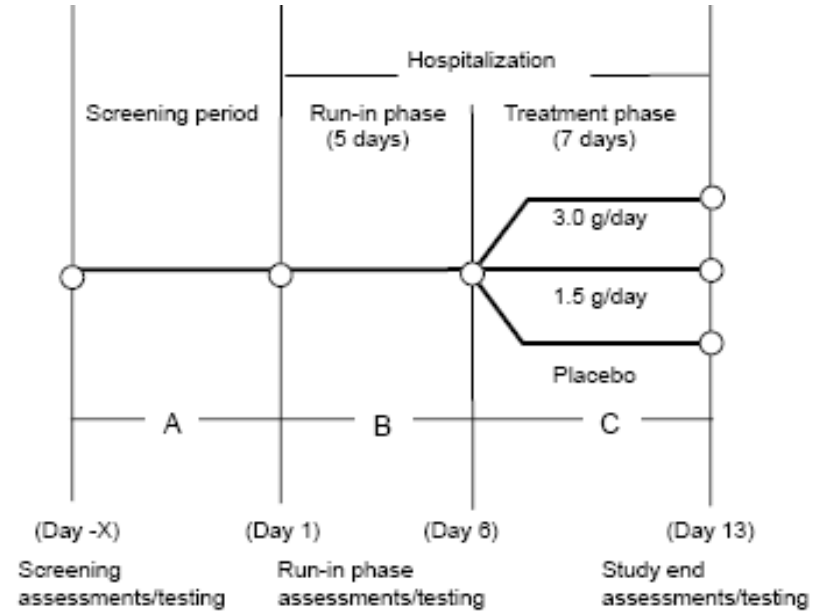
Concomitant use of other PEPs was not allowed from the beginning of the washout period through completion of the study. Use of proton pump inhibitors (PPIs), antacids, and H2-receptor blocking antihistamines, and prokinetic agents were permitted for use during the study only if they were in use at the time of enrollment. Patients who were not treated with (PPIs), antacids, and H2-receptor blocking antihistamines, and prokinetic agents were not allowed to take them during the whole study period (e.g., enrollment through final safety assessment). There is no comment in the protocol regarding whether dose changes of the preceding medicines were allowed during the study period. Medications not thought to interfere with the investigational agent were allowed. Doses and dates of use of concomitant medications were recorded in the CRFs.

6.1.3.2 New Adult PEI Study (Study S245.3.115)

6.1.3.2.1 Design, Treatment, and Population

The New Adult PEI study was a 13-day, randomized, double-blind, parallel-group, multi-center study to determine the efficacy and safety of SA-001 (Creon MMS) in adults with PEI due to chronic pancreatitis (CP, N=35) or pancreatectomy (PY, N=59). On completion of screening, patients underwent five days of single-blind placebo treatment to establish a Baseline CFA. Only patients with Baseline %CFA less than 80% were randomized to receive seven days of double-blind (DB) treatment with either placebo, Creon 1.5 gram/day (60,000 lipase U/day), or Creon 3.0 gram/day (120,000 lipase U/day). Efficacy was evaluated by the comparing mean change in CFA from baseline (placebo treatment) to CFA after seven days of DB treatment (i.e., placebo, 1.5 gram/day, and 3.0 gram/day). The overall study design is presented in Figure 1 below (electronically reproduced from the Sponsor's submission, volume 48, page 17,528).

Figure 1: New Adult PEI Study (S245.3.115), Study Phases



A: the screening period after obtaining informed consent until the study start
B: the 5-day placebo administration phase
C: the 7-day treatment phase with SA-001 3.0 g/day, 1.5 g/day, or placebo

6.1.3.2.2 Objectives and Outcomes Measures

The primary objectives of the study were the assessment of efficacy and safety. Efficacy was evaluated by comparing Baseline (placebo) CFA to CFA after seven days of DB treatment. Other efficacy parameters included change from Baseline in stool characteristics, and laboratory evaluation of nutritional parameters. Safety assessments included change from Baseline in history, physical examination, and laboratory assessments, and the occurrence during DB treatment of adverse events.

A secondary objective was to determine any difference between change in CFA between the low-dose and high-dose treatment groups.

6.1.3.2.3 Patient Eligibility/Inclusion and Exclusion Criteria

Patients were eligible for study participation if they were at least 20 years old, and had a diagnosis of either CP or PY with at least 7.5 g/day of stool fat at screening. Prior treatment with PEPs was allowed, but treatment must have ended no later than immediately prior to the beginning of the five-day placebo run-in phase.

Patients were excluded from study participation if their pre-study diet did not consist of at least 40 gram/day of dietary fat; if there was known clinically significant cardiovascular, gastrointestinal (other than primary disease), urogenital, or psychiatric/neurological disease; known allergy to the study drug or similar drug products; acute pancreatitis; superimposed acute pancreatitis, or if pregnant or lactating.

6.1.3.2.4 Concomitant and Prohibited Medications

Concomitant use of other PEPs was not allowed from the beginning of the placebo run-in phase through completion of the study. Use of proton pump inhibitors (PPIs), prokinetic agents, antacids, and H2-receptor blocking antihistamines were permitted for use during the study if they were in use at the time of screening, and the dose remained constant throughout the study.

6.1.3.3 Summaries of Clinical Trials Previously Reviewed: Prior Pediatric CF Study (S223.2.101), Prior Adult CF Study (S223.102), and Prior Adult CP Study (223.2.01)

Three short-term efficacy and safety studies were previously reviewed as part of the original NDA submission for Creon, and only brief summaries from the original clinical reviews are provided here.

6.1.3.3.1 Prior Pediatric CF Study (S223.2.101)

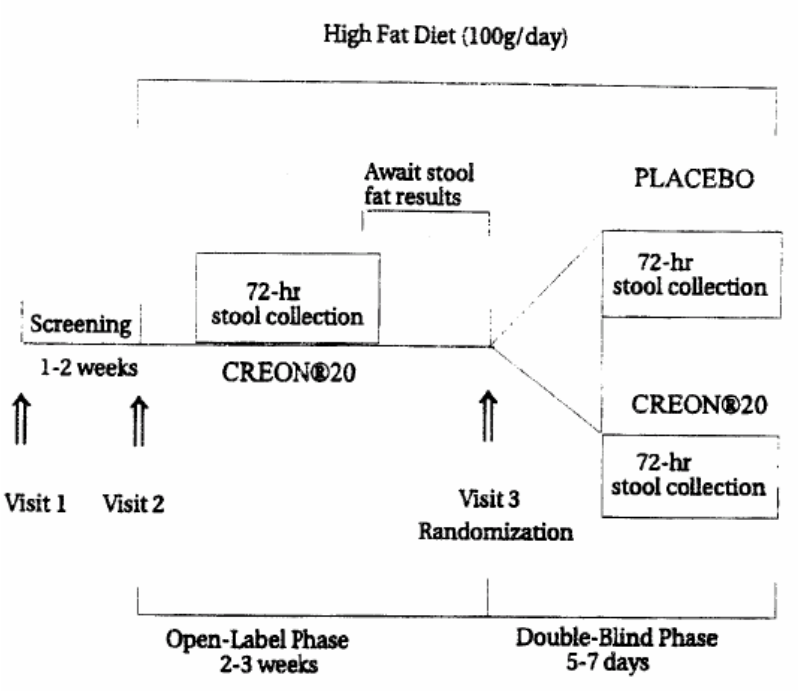
6.1.3.3.1.1 Design, Treatment, Dose, and Population

The Prior Pediatric CF Study was a randomized-withdrawal, double-blind, placebo-controlled, multi-center study in patients with CF, ages 7 to 17 years. The study was four to six weeks in duration, including a one- to two-week screening period, a two- to three-week open-label Creon treatment phase, and five- to seven-day double blind phase wherein patients were treated with either Creon or placebo. Forty-seven patients were enrolled and treated with open-label Creon® 20 (MMS; 20,000 lipase units) with individualized dosing. All patients were treated with a high-fat diet (at least 100 grams of fat/day) from the beginning of the open-label phases through the completion of the study.

The first of two 72-hour stool collections for CFA was begun after at least 48 hours of high-fat diet during the open-label Creon treatment phase. After completion of stool collection for the first CFA, patients continued the same individualized Creon dose and high-fat diet for two to three weeks. Patients with initial CFA above 80% while on a high-fat diet and open-label Creon treatment were then randomized into the double-blind phase of the study (total N=38: 18 patients randomized to Creon MMS, and 19 patients to placebo; treatment groups are named by treatment they were randomized to in the DB phase of the study). The second 72-hour stool collection for CFA was begun after 48 hours of treatment during the double-blind phase.

Treatment effect for individual patients was assessed by comparing change in CFA from the open-label treatment phase to the double-blind treatment phase. Primary efficacy was assessed by comparing the mean change in CFA between the Creon and placebo treatment groups during the open-label (Creon treatment) phase compared to the DB (Creon or placebo treatment) phase. Secondary efficacy parameters included change in stool frequency, stool consistency, and clinical global improvement (CGI) scores from the open-label treatment phase compared with the double-blind phase. A diagram of the overall study design is presented in Figure 2 below (electronically reproduced from prior clinical review by Dr. Gibril, 09-December-2003)

Figure 2: Prior Pediatric Cystic Fibrosis Study (S223.2.101), Study Phases



6.1.3.3.1.2 Objectives and Outcomes Measures

The primary objective of the study was to evaluate the effectiveness of Creon® 20 compared to placebo in the treatment of steatorrhea in CF patients with PEI. Efficacy was evaluated by comparing CFA from the open-label, Creon-treatment phase to CFA from the double-blind treatment (with Creon® 20 or placebo) phase. The secondary objectives were to compare the effect of treatment on frequency of bowel movements, stool consistency, and CGI, and assessments of safety during administration of Creon® 20 capsules. Safety parameters were summarized by treatment group and included any changes in physical examinations and vital signs, and routine clinical laboratory examination (including urine and serum uric acid monitoring), and the occurrence during treatment with Creon of adverse events.

6.1.3.3.1.3 Patient Eligibility/Inclusion and Exclusion Criteria

Patients were eligible for study participation if they were 7 to 17 years old, had a diagnosis of CF (by two sweat chloride tests), had clinical symptoms of PEI, and had a history of steatorrhea. Patients were excluded from study participation if they had a forced expiratory lung volume in one second (FEV1) of less than 25% or clinically severe pulmonary disease, required the ingestion of medium chain triglycerides as nutritional supplements, had abnormal serum uric acid on screening, or had concurrent use of non-study PEPs. Patients could not have received antacids or other acid suppressants, prokinetic drugs, or antibiotics known to have caused diarrhea in the 30 days prior to screening.

6.1.3.3.2 Prior Adult CF Study (S223.2.102)

The design of the Prior Adult CF study is identical to the Prior Pediatric CF study summarized above, except that patients in this study were 18 years and older at time of enrollment. Fifty patients were enrolled and treated with open-label Creon® 20 and a high-fat diet, and 36 patients were proceeded to the randomized double-blind phase of the study (total N=36: 18 patients randomized to Creon MMS, and 18 patients to placebo).

6.1.3.3.3 Prior Adult CP Study (223.2.01)

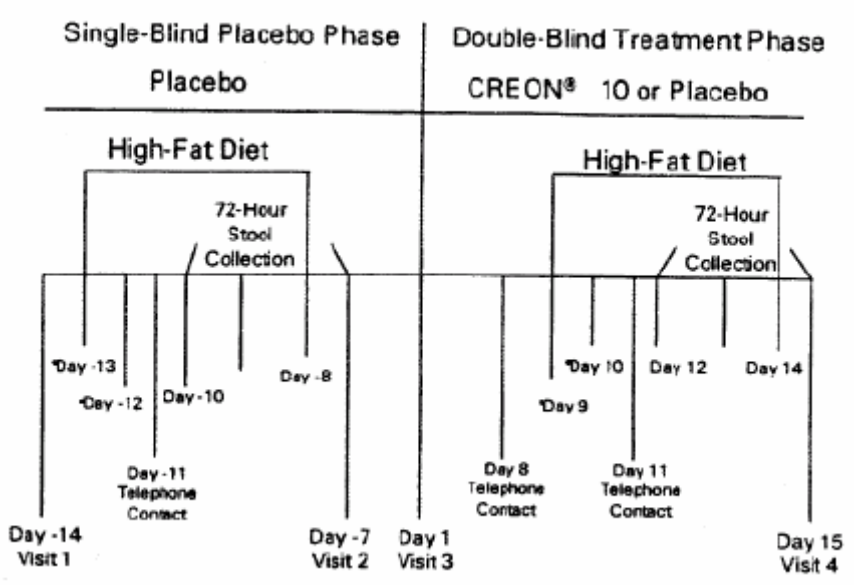
6.1.3.3.3.1 Design, Treatment, Dose, and Population

The Prior Adult CP study was a randomized, double-blind, placebo-controlled, study of Creon® 10 (MMS; 10,000 lipase units) in adult patients with CP, ages 38 to 74 years. The study consisted of two consecutive, two-week, outpatient phases: a single-blind, placebo run-in/wash-out phase, and a randomized, double-blind treatment (Creon or placebo) phase. Patients were to consume a high-fat diet from the beginning of the single-blind placebo phase through completion of the double-blind treatment phase.

Sixty-four patients entered the single-blind, placebo run-in phase. Since many of the patients were receiving treatment with PEPs prior to study entry, this phase served as a PEP wash-out phase. Patients with CFA less than 80% or stool fat greater than 10 gram/day, or both, during the placebo run-in phase proceeded to the double-blind treatment phase, where they were randomized to treatment with either Creon® 10 or placebo (total N=27; 13 patients randomized to Creon MMS, and 14 patients to placebo). The Creon dose during the study was four capsules (40,000 lipase units) per meal and two capsules (20,000 lipase units) per snack, with a minimum of 10 capsules (100,000 lipase units) per day and a maximum of 24 capsules (240,000 lipase units) per day.

Treatment effect for individual patients was assessed by comparing change in CFA from the single-blind placebo phase to the double-blind treatment phase (Creon® 10 or placebo). Primary efficacy was assessed by comparing the mean change in CFA between the Creon treatment and placebo groups during the double-blind phase (Creon or placebo) compared to the single-blind placebo phase. The Primary efficacy endpoint was difference in mean CFA between the placebo and treatment groups during the double-blind treatment phase. The study phases are presented in Figure 3 below (electronically reproduced from prior clinical review by Dr.Gibril, 09-December-2003).

Figure 3: Prior Adult Chronic Pancreatitis Study (223.2.01), Study Phases



6.1.3.3.3.2 Objectives and Outcomes Measures

The objective of the study was to compare the efficacy of Creon®10 versus placebo on change in CFA from the single-blind placebo phase compared to the double-blind treatment phase. Safety was assessed by the evaluation of safety variables including change from Baseline in medical history, physical examinations, and laboratory analyses, and the occurrence of adverse events.

6.1.3.3.3.3 Patient Eligibility/Inclusion and Exclusion Criteria

Patients were eligible for study participation if they had a clinical history consistent with CP, and confirmation of CP diagnosis by one of the following criteria: computed-tomography, endoscopic retrograde cholangiopancreatography (ERCP), or pancreatic calcification on abdominal x-ray or ultrasound. Patients must also have had evidence of active PEI demonstrated by at least one of the following: steatorrhea, secretin test, serum trypsin, or PABA urinary test, and the use of any PEP for the entire six months preceding study entry. Patients were excluded from study participation if they had CF, severe systemic disease, or had been diagnosed with an ileus, acute abdomen, or acute pancreatitis within the two months preceding study entry.

6.1.4 Efficacy Findings

Detailed reviews of the efficacy findings from the New Infant CF Study and New Adult PEI studies were performed, and are summarized in the Appendix in the Individual Study Reports section.

The key efficacy findings from the New Infant CF and the New Adult PEI studies are summarized below. The determination of efficacy is based solely on primary efficacy endpoints and results of secondary efficacy measures are not discussed. The reader is directed to the individual study reports

in the Appendices of this document for discussion of secondary endpoints of the New Infant CF and New Adult PEI studies.

Likewise, the key efficacy findings from the previously reviewed Prior Pediatric CF, Prior Adult CF and Prior Adult CP studies were based solely on primary efficacy endpoints and the results of secondary efficacy measures of those three studies are not discussed.

6.1.4.1 New Infant CF Study (S248.3.003)

The primary efficacy endpoint in the New Infant CF study was change from Baseline (no-treatment) CFA compared to Creon treatment period CFA in the Intent-to-treat (ITT) population.

All twelve infants with PEI due to CF were successfully screened and enrolled, completed the study, and were included in the ITT analysis. There were five males and seven females, ranging in age from one through 23 months. For the primary endpoint, there was a clinically meaningful increase in CFA from Baseline compared to treatment with Creon. The mean Baseline CFA was 58%, the Creon treatment period mean CFA was 85%, and change in mean CFA was 27% (95% C.I. [12.9, 40.4]).

Because treatment effect has been reported to be more clinically apparent in patients with lower Baseline CFA,[1] this Reviewer also performed an unplanned subgroup analysis comparing the mean change in CFA from Baseline in patients with a Baseline CFA <60% (N=4), and in patients with a Baseline CFA ≥60% (N=8). For the subgroup of patients with a Baseline CFA <60%, the mean Baseline CFA was 41%, the mean increase in CFA while on Creon treatment was 43% (95% C.I. [-0.9, 86.1]). Although the results show a large increase in mean CFA in these patients from Baseline compared to Creon treatment, the mean change in CFA is not statistically significant, most likely due to the small number of patients in this subgroup. For the subgroup of patients with a Baseline CFA ≥60%, the mean Baseline CFA was 66%, and the mean change in CFA was 19% (95% C.I. [6.8, 30.6]). These findings are clinically meaningful but not statistically significant due to the small number of patients studied.

This Reviewer concludes the findings are supportive of efficacy. The results of the primary efficacy analysis and for the subgroup analyses (by Baseline CFA <60% or ≥60%) are summarized in the following table (from Dr. Castillo's Review):

Table 2: Study S248.3.003; Change in CFA (%) by Baseline CFA (%) Category for ITT Population

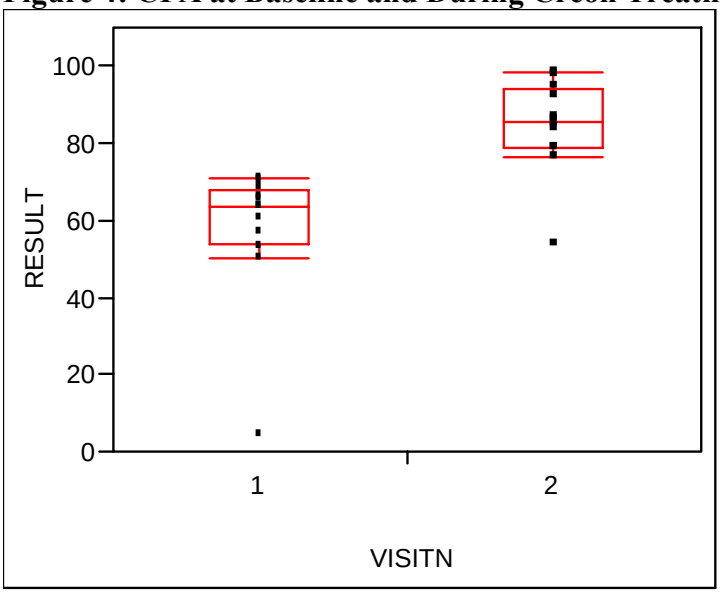
	All Patients	Baseline CFA<60	Baseline CFA≥60
n	12	4	8
Baseline mean (%)	58.0	41.4	66.4
Mean change from baseline (95% C.I.)	26.7 (12.9, 40.4)	42.6 (-0.9, 86.1)	18.7 (6.8, 30.6)

Source: Statistical Reviewer's analysis

The results for CFA at Baseline (no-treatment) and for CFA during Creon treatment for the ITT population are presented graphically in the following figure, Figure 4.

Explanation of Figure 4: The VISITN 1 column represents Baseline encounters and the VISITN 2 column represents encounters during Creon treatment. Each data point along the Y (RESULT) axis represents an individual patient's CFA reported in percent units. The bottom of each closed box delimits the lowest 25th percentile of CFA and the top of each box delimits the upper 75th percentile of CFA. The bottom line under each box delimits the lower 5th percentile of CFA and the topmost line above each box delimits the upper 95th percentile of CFA. The horizontal line within each box represents the median CFA for each treatment period. The dots below the boxes are outliers.

Figure 4: CFA at Baseline and During Creon Treatment in the ITT Population



RESULT: Coefficient of Fat Absorption (CFA)
VISITN: Baseline visit (1), treatment period visit (2).

In summary, a clinically meaningful increase in CFA was demonstrated for the ITT population. Increase in CFA while on treatment compared to no-treatment baseline tended to be greatest in patients with lowest Baseline CFA. These findings provide clinically meaningful evidence that Creon MMS (CMP) augments pancreatic lipase activity. This Reviewer concludes that the results support the efficacy of Creon for infants with CF-related PEI at the dose studied.

6.1.4.2 New Adult PEI Study (S245.3.115)

The primary efficacy endpoint in the New Adult PEI study was change in CFA from non-treatment (single-blind placebo) baseline phase compared to the DB (Creon or placebo treatment) phase for the ITT population.

Of 156 patients who were screened, 95 patients were enrolled and one patient withdrew consent prior to starting the study, leaving 94 patients in the ITT. Of these 94 patients, 30 patients were randomized to treatment in the placebo group, 31 patients in the 1.5 gram/day (low-dose) group, and 33 patients in the 3.0 gram/day (high-dose) group. Baseline demographic data showed that 35 patients had chronic pancreatitis and 59 had pancreatectomy. All patients were Asian, and 81% of patients were male. Seventy-nine patients had a history of PEP exposure prior to study entry. There were no important differences between the treatment groups by Baseline demographic criteria.

Results for the primary efficacy endpoint, change in CFA from non-treatment (single-blind placebo) Baseline phase compared to the DB (Creon or placebo treatment) phase for the ITT population, showed that change in mean CFA from Baseline to DB treatment was 4% for the placebo group, 11% for the low-dose group, and 16% for the high-dose group. Compared to the placebo group, mean CFA change for the low-dose group was 7% (p-value = 0.144), and mean CFA change in the high-dose group was 12% (p-value = 0.015). The clinical meaning of these results is unclear due to an unplanned interim analysis discussed at the end of this section. This Reviewer concludes that these findings can not be used to support efficacy.

This Reviewer also performed subgroup analyses of the primary endpoint for the PY and CP subgroups. For the CP subpopulation, change in mean CFA from Baseline to DB treatment was 5% for the placebo group, 9% for the low-dose group and 7% for the high-dose group. Compared to the placebo group, mean CFA change for the low-dose group was 4% (p-value = 0.540), and mean CFA change in the high-dose group was 2% (p-value = 0.781). The clinical meaning of these results is unclear due to an unplanned interim analysis discussed at the end of this section. This Reviewer concludes that these findings can not be used to support efficacy.

For the PY subpopulation, change in mean CFA from Baseline to DB treatment was 3% for the placebo group, 12% for the low-dose group and 20% for the high-dose group. Compared to the placebo group, mean CFA change for the low-dose group was 9% (p-value = 0.180), and mean CFA change in the high-dose group was 18% (p-value = 0.011). The clinical meaning of these results is unclear due to an unplanned interim analysis discussed at the end of this section. This Teviewer concludes that these findings can not be used to support efficacy.

The preceding findings are summarized in Table 3 below (from Dr. Castillo's review).

Table 3: New Adult PEI Study—Change in Coefficient of Fat Absorption for All Patients by Diagnosis, ITT Population[1]

	Creon 1.5 g/day [3]	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.) [2]	7.1 (4.8)	11.6 (4.7)	
p-value for Mean Treatment Difference	0.144	0.015	
Chronic Pancreatitis			
n	11	11	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	

[1] Source: Statistical Reviewer's Analysis based on ANOVA model with treatment as factor.
[2] Standard Error
[3] One patient included in the FAS in the 1.5 g/day group did not have treatment period CFA performed/recorded thereby reducing n from 31 to 30 patients.

The study results showed a significant increase in CFA compared to the placebo group was demonstrated for the high-dose Creon treatment group for the overall (ITT) study population. A significant increase in mean CFA compared to the placebo group was also demonstrated for the high-dose Creon treatment group for the PY subpopulation; however, the increase in CFA did not reach 30%. No significant change in CFA compared to the placebo group was demonstrated for the low-dose group for the overall study population, or in either the PY or CP sub-populations. No difference in mean change in CFA in either the low- or high-dose groups compared to the placebo group seen in the CP subpopulation.

Of note, there were seven patients in any Creon CMP treatment group with a Baseline CFA less than 40%, including five patients in high dose PY sub-population and two patients in the low dose PY sub-population. No patients in the CP sub-population who received Creon CMP had Baseline CFA less than 40%.

It was additionally noted that the mean Baseline CFA in the placebo-treated patients was lower overall, and especially, in the CP sub-population, as compared to the high-dose Creon treatment group (and to a lesser extent the low-dose Creon treatment group). Specifically, mean Baseline CFA in the high-dose CP sub-population was 78%, which was about 21% higher than the placebo-treated CP sub-

population, and 16% higher than the high-dose PY sub-population. These findings indicate that based on mean CFA levels at Baseline: 1) the potential for the high-dose Creon CP sub-population to respond to treatment was lower than in the placebo-treated CP sub-population, which may account for the lack of response seen in that group; and 2) the potential to respond was higher in the high-dose PY sub-population, which may explain the trend toward increase in CFA with treatment in this sub-population. Thus, this Baseline mean CFA imbalance may have affected the overall results for the study, as the high-dose Creon treatment had a lower capacity to respond, resulting in a lower likelihood of detecting a treatment difference between the groups.

In summary, a significant increase in mean CFA in the high-dose Creon group compared to placebo was demonstrated in the overall ITT population. No significant difference in mean CFA compared to placebo was demonstrated in the low-dose Creon group (overall or by subpopulation), or in the CP subpopulation with either Creon dose.

Amendments critical to the efficacy review are now described:

Two related protocol amendments critical to the review are now described. One amendment increased the size of each treatment group from 18 to 25 patients. The Sponsor states that the protocol was amended because a prior amendment allowed for a blinded, un-planned interim analysis to be performed. The blinded analysis was performed on the subset of patients who had at that time completed both the single-blind non-treatment phase and the double-blind (treatment or placebo) phase.

The Sponsor reports that the interim analysis suggested that the original study was underpowered to detect the expected change in CFA between the Creon-treated groups compared to the placebo group. Therefore, group size was increased from 18 to 25 patients per treatment arm to ensure a 90% power at a two-sided significance level of 5%. The Statistical Reviewer, Dr. Sonia Castillo, concludes that since the interim analysis was not pre-specified and the potential effects on measures of statistical success were not provided, no statistical inferences of the efficacy results can be made.

A trend towards increased CFA (primary efficacy point) with high-dose treatment in the overall population and the high-dose PY subgroup is suggested. However, this Reviewer concludes that the efficacy findings of the New Adult PEI cannot be used to support efficacy of Creon CMP for the treatment of PEI due to PY or CP due to the statistical issues outlined in the preceding paragraph. Further, efficacy was not demonstrated in the low-dose treatment arms, or in the CP group at any dose.

6.1.4.3 Efficacy results of previously reviewed pivotal trials.

6.1.4.3.1 Prior Pediatric CF Study (S223.3.101)

The Prior Pediatric CF study was a double-blind, placebo-controlled, randomized-withdrawal study of Creon CMP in pediatric patients with CF, ages seven to 17 years. The primary efficacy endpoint was change in CFA from Baseline (OL Creon treatment) compared to CFA on DB treatment (Creon or placebo). Patients must have had a Baseline CFA of <80% to enter to DB phase of the study. Forty-

seven patients entered the study and completed the OL Creon treatment phase, and 38 patients qualified for randomization to the DB treatment phase of the study. The ITT population included 37 patients: One patient withdrew prior to randomization, 18 patients were randomized to Creon (Creon group) and 19 were randomized to placebo (placebo group). The mean Creon® 20 dose taken during the double-blind phase was 7,855 lipase units/kg/day. Gender distribution across the two treatment groups was approximately even. Patient ages ranged from 7 to 17.9 years, and racial representation was 95% Caucasian, 2% Black, and 2% Other.

The results show that both treatment groups had a similar mean Baseline CFA. The placebo group had a mean CFA of 86% and the Creon group had a mean CFA of 87%. After randomized-withdrawal during the DB treatment phase, the placebo group had a mean CFA of 52%, which is a decrease in mean CFA of 34. In the DB treatment phase, the Creon group had a mean CFA of 84%, which was essentially unchanged from Baseline (change in mean CFA in the Creon group of -3). The overall results for the primary efficacy endpoint show a statistically significant and clinically meaningful mean difference between the two groups in favor of Creon treatment, with CFA 35% higher in the treatment arm (p-value <0.001). The results are summarized Table 4 below (electronically reproduced from previous clinical review, by Dr. Gibril, September 2003).

Table 4: Prior Pediatric CF Study, Primary Endpoint Result (Change in Mean CFA

	Mean CFA (%)						
Protocol	**Open-label (OL) (Run-in phase) treatment**		**Double-blind (DB) treatment**		**Change from OL to DB**		**p-value***
	Placebo N= 19	Creon N= 18	Placebo N=19	Creon N=18	Placebo N=19	Creon N=18	
S2233101	86%	87%	52%	84%	-34%	-3%	<0.001
*p-value for comparison of the two treatment groups for change in CFA from OL to DB treatment							

This Reviewer agrees with conclusions of the prior clinical review team that the results demonstrate a statistically significant and clinically meaningful benefit for the use of Creon CMP in children 7 through 17 years old with PEI due to CF.

6.1.4.3.2 Prior Adult CF Study (S223.3.102)

The Prior Adult CF study was a double-blind, placebo-controlled, randomized-withdrawal study of Creon CMP in adult patients with CF. The primary efficacy endpoint was change in CFA from Baseline (OL Creon treatment) compared to CFA on DB treatment (Creon or placebo). Patients must have had a Baseline CFA of <80% to enter to DB phase of the study. Fifty patients entered the study and completed the OL Creon treatment phase, and 36 patients qualified for randomization to the DB treatment phase of the study. The ITT population was comprised of all 36 qualifying patients: 18 patients were randomized to Creon (Creon group) and 18 were randomized to placebo (placebo group). The mean Creon® 20 dose taken during double-blind phase was 4,537 lipase units/kg/day. Baseline gender composition was 40% female and 60% male, which was approximately evenly distributed across the treatment groups. Patient ages ranged from 18 to 53 years, and racial representation was 100% Caucasian.

The results show that both treatment groups had a similar mean Baseline CFA. The placebo group had a mean CFA of 88% and the Creon group had a mean CFA of 89%. After randomized-withdrawal during the DB treatment phase, the placebo group had a mean CFA of 51%, which is a decrease in mean CFA of 35. In the DB treatment phase, the Creon group had a mean CFA of 87, which was essentially unchanged from Baseline (change in mean CFA in the Creon group of -2). The overall results for the primary efficacy endpoint show a statistically significant and clinically meaningful mean difference between the two groups in favor of Creon treatment, with CFA 32% higher in the treatment arm (p-value <0.001). The results are summarized in Table 5 below (electronically reproduced from previous clinical review, by Dr. Gibril, September 2003).

Table 5: Prior Adult CF Study, Primary Endpoint Result (Change in Mean CFA)

	Mean CFA (%)						
Protocol	**Open-label (OL) (Run-in phase) treatment**		**Double-blind (DB) treatment**		**Change from OL to DB**		**p-value***
	Placebo N=18	Creon N=18	Placebo N=18	Creon N=18	Placebo N=18	Creon N=18	
S2233102	88%	89%	51%	87%	-37%	-2%	<0.001
*p-value for comparison of the two treatment groups for change in CFA from OL to DB treatment							

This Reviewer agrees with conclusions of the prior clinical review team that the results demonstrate a statistically significant and clinically meaningful benefit for the use of Creon CMP in adults, 18 years and older, with PEI due to CF.

6.1.4.3.3 Prior Adult CP Study (223.2.01)

The Prior Adult CP study was a randomized, double-blind, placebo-controlled study of Creon CMP in adult patients with CP. The primary efficacy measure was change in CFA from the single-blind (SB) placebo phase compared to CFA during DB phase (placebo or Creon treatment). The study endpoint was the comparison of the difference in mean change in CFA between the placebo and treatment groups. Patients must have had a Baseline (single-blind placebo treatment) CFA of <80% or stool fat ≥10 g/day to enter to DB phase of the study. Sixty-four patients entered the single-blind (placebo) treatment phase of the study, and 27 patients underwent randomization to the DB treatment phase of the study: 13 patients were randomized to Creon treatment (Creon group) and 14 patients were randomized to placebo treatment (placebo group). One patient in the Creon group was excluded from the efficacy analysis due to missing data (lost stool collection), which reduced the ITT population to 26 patients. The mean Creon® 10 dose taken by the treatment group was 1,780 units/kg/day. Patient ages ranged from 31 to 74 years. There were nine females and 18 males, and there were 17 Caucasian and ten Black patients. There were no imbalances between the treatment groups by Baseline demographic data.

The results show that both treatment groups had a similar mean Baseline CFA. The placebo group had a mean Baseline CFA of 56% and the Creon group had a mean Baseline CFA of 50%. In the

randomized DB treatment phase, the placebo group had a mean CFA of 68%, which was an increase in mean CFA of +12%. In the DB treatment phase, the Creon group had a mean CFA of 87, which was an increase in mean CFA of +37%. Comparison between the two treatment groups showed that the Creon group had a larger mean increase in CFA compared to the placebo group that was clinically meaningful and statistically significant (p=0.0185). These results are summarized in Table 6 below (electronically reproduced from previous clinical review, by Dr. Gibril, September 2003).

Table 6: Prior Adult CP Study (), Primary Endpoint Results (Change in Mean CFA

	Mean CFA (%)						
Protocol	**Single-blind (SB) placebo phase**		**DB treatment phase**		**Change from SB to DB**		
	Placebo N=14	Creon N=12	Placebo N=14	Creon N= 12	Placebo N=14	Creon N= 12	**p-value***
223.2.01	56%	50%	68%	87%	12%	37%	0.0185
*p-value for comparison of the two treatment groups for mean change in CFA from SB to DB treatment							

This Reviewer concurs with the previous clinical review team's conclusions that the Prior Adult CP study provides statistically significant and clinically meaningful evidence of clinical efficacy for Creon compared to placebo for mean change in CFA from single-blind (placebo) to DB treatment.

6.1.5 Efficacy Conclusions

The efficacy of Creon TbMP has not been demonstrated.

The Sponsor intends to market Creon TbMP, for which no efficacy and safety clinical trials have been conducted. The Sponsor states that data from the five clinical short-term efficacy and safety studies demonstrate that Creon CMP is effective in the treatment of steatorrhea due to PEI in patients with CF, CP, and PY. The three previously reviewed studies support efficacy. The New Infant CF Study provides supportive evidence of efficacy; however, the findings do not reach clinical significance due to the small study size. The New Adult PEI study does not provide convincing evidence of efficacy. Lastly, the Bridging study, conducted for the purpose of demonstrating the comparability of the Creon CMP and TbMP products, failed to demonstrate the clinical comparability of the two products. Therefore, the efficacy of Creon TbMP has not been demonstrated.

In this CR amendment, two new short-term efficacy and safety studies were submitted that were amenable to substantive review. These two studies, the New Infant CF study and the New Adult PEI, showed the following results:

- The New Infant CF study evaluated change in CFA from Baseline (non-treatment) phase to Creon treatment phase in 12 infants, ages one to 24 months, with PEI due to CF. Mean increase in CFA was 27% (95% C.I. 12.3, 41.1), and the increase in CFA with treatment was greatest in four patients with Baseline CFA below 40%. The Statistical Reviewer concluded that the small study size precluded statistical inferences. Nevertheless, these findings are

consistent with results seen in children and adults in the Prior Pediatric CF and Prior Adult CF studies.

This Reviewer concludes that while statistical inferences can not be drawn, the results are clinically meaningful. In conclusion, this study supports the short-term efficacy of Creon treatment in infants with CF, and use down to one month of age is supported and may be reflected in labeling.

- The New Adult PEI study evaluated change in CFA from non-treatment (SB placebo) phase to DB treatment (Creon or placebo) phase in adults with PEI due to CP or PY. Compared to the placebo group, the mean CFA change for the low-dose group was 7% (p-value = 0.144), and mean CFA change for the high-dose group was 12% (p-value = 0.015). In the PY sub-population, mean increase in CFA for the high-dose group compared to placebo was 18% (p-value = 0.011), and in the CP sub-population was 2% (p-value = 0.781).

  Overall, the study results show a significant increase in mean CFA in the high-dose Creon group compared to placebo in the ITT population and in the PY sub-population. No significant difference in mean CFA compared to placebo was demonstrated in the low-dose Creon group (overall or by sub-population), or in CP patients treated with either low-dose or high-dose Creon CMP.

  Imbalances between the treatment groups by Baseline mean CFA may have affected the overall results of the study. The placebo group had the lowest Baseline CFA and the high-dose Creon treatment group had the highest CFA. This imbalance may have affected the overall study results since there was a lower likelihood of detecting a difference between the placebo and high-dose Creon groups as the high-dose group had a lower capacity to respond to active treatment.

  The Sponsor performed a non-pre-specified interim analysis, which suggested that the original study was underpowered to detect the expected change in CFA between the Creon-treated groups compared to the placebo group. Therefore, group size was increased from 18 to 25 patients per treatment arm. The Statistical Reviewer, Dr. Sonia Castillo, concludes that since the interim analysis was not pre-specified and the potential effects on measures of statistical success were not provided, no statistical inferences of the efficacy results can be made.

  Thus, it is the assessment of this Reviewer that the clinical findings of the New Adult PEI do not support the efficacy of Creon CMP for treatment adult patients with PEI due to PY or CP.

Three clinical short-term efficacy and safety studies were previously reviewed during the original NDA review cycle for Creon. These studies were assessed by the Clinical Review Team as having demonstrated statistically significant and clinically meaningful evidence of clinical efficacy for Creon (by change in CFA) in pediatric (ages 7 years and older) and adult patients with CF, and in adult patients with CP. These three studies showed the following results:

- In the Prior Pediatric CF Study (S2233101) after randomized-withdrawal from Baseline Creon treatment to DB treatment with placebo or Creon, mean CFA in the Creon treatment group was 31% higher than mean CFA in the placebo group (p-value < 0.001). These results showed a statistically significant and clinically meaningful benefit in favor of Creon treatment for difference in mean CFA between the Creon and placebo groups in pediatric patients with CF.

- In the Prior Adult CF Study (S2232102) after randomized-withdrawal from Baseline Creon treatment to DB treatment with placebo or Creon, mean CFA in the Creon treatment group was 35% higher than mean CFA in the placebo group (p-value < 0.001). These results showed a statistically significant and clinically meaningful benefit in favor of Creon treatment for difference in mean CFA between the Creon and placebo groups in adult patients with CF

- In the Prior Adult CP Study (223201), mean change in CFA from Baseline (SB placebo treatment) to DB treatment (Creon or placebo) was 25% higher in the Creon treatment group than in the placebo group (p-value <0.0185). These results showed a statistically significant and clinically meaningful benefit in favor of Creon treatment for difference in mean CFA between the Creon and placebo groups in adult patients with CP.

In conclusion, it is the overall assessment of this Reviewer that data from three short-term clinical efficacy and safety studies conducted in pediatric and adult patients with CF, and adult patients with CP support the effectiveness of Creon CMP treatment of steatorrhea in patients with EPI, and that Creon's effectiveness appears to be greatest in the most severely affected patients (i.e., patients with the lowest Baseline CFA). Results from the New Infant CF study were supportive of the clinical effectiveness of Creon CMP in the treatment of steatorrhea in infants with CF, ages one to 24 months these patients, and the results from this study were consistent with the results seen in clinical studies in older pediatric and adult patients. These findings support the labeling of Creon CMP for the treatment of steatorrhea in patients with EPI, ages one month to adult. The results from the New Adult PEI study cannot be used to support the effectiveness of Creon CMP in the treatment of EPI, due to problems with study conduct, and because of the results of the study were not clinically meaningful.

The Sponsor intends to market the Creon TbMP. However, no efficacy and safety clinical trials have been conducted to date with the Creon TbMP. The Bridging study that was submitted to the CR amendment, and was conducted for the purpose of demonstrating the comparability of the Creon CMP and TbMP products, failed to demonstrate the clinical comparability of the two products. Thus, the efficacy and safety results from studies with the Creon CMP cannot be used to support the clinical efficacy and safety of the Creon TbMP. Therefore, the efficacy (and safety) of the Creon TbMP for the treatment of steatorrhea in patients with EPI has not been demonstrated, and the information submitted in this CR amendment does not support the approval of Creon TbMP.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This Complete Response (CR) amendment includes safety information from the NDA Safety Update (Integrated Safety Summary; ISS). This ISS contains information from 57 clinical studies conducted between July 1985 and May 2006, and performed with Creon MMS (CMP) or other formulations that are no longer marketed (e.g., Creon MS). All patients who received at least one partial dose of Creon MMS and Creon MS were included in the safety population. Safety reporting is through 30-June-2006, and there were no ongoing studies at the time of submission.

The safety of the TbMP has not been evaluated in clinical trials, with the exception of single-dose Creon TbMP administration to nine patients in the Bridging study. Since the clinical comparability of the Creon CMP to the TbMP was not demonstrated in the Bridging study, safety data obtained with the CMP can not be solely relied upon to establish the safety of the TbMP.

Of the 57 studies in the ISS, 52 are multiple-dose studies and five are single-dose studies. Safety information from 12 of the 57 studies is submitted for the first time in this CR amendment. Seven studies were not incorporated into the ISS due to data quality issues (e.g., inadequate methods for data collection, and incomplete safety datasets), and were not included in this safety review. Therefore, the ISS contains safety information from 50 studies.

Sufficient safety information was provided in the CR amendment to allow substantive review of the two newly submitted studies for safety: the New Infant CF Study and the New Adult PEI Study. These studies have been individually reviewed for safety by this Reviewer.

Because children with CF are an important treatment population for the PEPs, this Reviewer also assessed the safety of Creon MMS in children with CF. Insufficient safety information was provided in the CR amendment to allow substantive review of all studies of Creon MMS (CMP) in children; however, there was sufficient information available to permit a safety review of three pediatric CF safety studies (e.g., electronic safety datasets) in addition to the Infant CF Study. Thus, this Reviewer performed a pooled safety analysis of four CF pediatric studies, including the New Infant CF Study, and three additional open-label safety studies of Creon CMP in pediatric CF patients: the Prior Infant CF Safety, Prior Pediatric CF Safety Study, and Prior Young Adult CF Safety Study. These three additional studies included pediatric CF patients from six months through 18 years of age, and included approximately 150 patients. The designs of these three additional studies are described as follows:

The Prior Infant CF Safety Study (S245.3118) was an open-label, randomized, cross-over study of Creon MMS and a Creon formulation designated “Creon for Children” (CFC; a non-US marketed formulation of MMS) in infants with PEI due to CF, six to 36 months old. The primary outcome measure was parental preference of either formulation. Forty (40) patients were randomized and underwent a non-treatment period of one to two weeks. Nineteen patients received CFC for two weeks followed by Creon MMS for two weeks (CFC>MMS), and 21 patients received Creon MMS

for two weeks followed by CFC for two weeks (MMS>CFC). One patient randomized to CFC>MMS withdrew during the first treatment period due to nausea, vomiting, and diarrhea. Mean exposure to CFC and Creon MMS was 14 days each.

The Prior Pediatric CF Safety Study (S245.3105) was an open-label, randomized, cross-over study of Creon 10,000 (Creon MMS) or Creon 8,000 (Creon MS) in children with PEI due to CF, three to 17 years old (the individual study report is not available for review and this summary is taken from pages 8,479 and 8,480 of volume 24 of the sponsor's CR amendment; further details were not available). The primary efficacy outcome measure was comparison of CFA between the two treatment groups. There was no placebo treatment group and there was no open-label non-treatment period. Following a two-week run-in period with Creon 8,000 MS, patients received either four weeks of Creon MMS followed by four weeks of Creon MS, or four weeks of Creon MS followed by four weeks of Creon MMS. Fifty-nine (59) patients were entered in the study, including 11 patients less than 7 years old, 28 patients ages 7 to less than 12 years old, and 20 patients ages 12 to less than 18 years old. Only 57 of these 59 patients received Creon MMS.

The Prior Young Adult CF Safety Study (K245.5004) was a randomized, double-blind, cross-over study in patients four years and older with CF (N=34) that compared the CFA during treatment with Creon MMS to Creon MS. There was no placebo treatment group and there was no open-label non-treatment period. The study design included a two- to three-week run-in period with Creon 8,000 MS followed by two crossover periods of two weeks each, in which Creon 10,000 MMS and Creon 8,000 MS were given in random order. Thirty-four (34) patients were entered in the study, including 14 patients ages 7 to less than 10 years old, 14 patients ages 10 to less than 18 years old, and six patients ages 18 to 31 years. Exposure to Creon MMS was for two weeks.

These three studies were reviewed and summarized for safety only. Substantive review for efficacy of these three trials was not possible due to lack of uniform drug treatments, dosage regimens, and controls.

Table 7 below lists the individual studies that were reviewed and summarized for safety in this CR amendment review.

Table 7: Safety Items Reviewed

Item Reviewed	Full or Summary Review	Comment
Integrated Summary of Safety (ISS)	Full	
New Infant CF Study (S248.3.003)	Full	Open label (OL), single-arm study in 12 infants, age 1-24 months. 7-10 day placebo (P) Baseline (BL) phase, followed by OL treatment with Creon MMS for 8 weeks. Safety measures were collected from start of placebo period through end of 8 weeks of treatment.
New Adult PEI Study (S245.3115)	Full	2-3 weeks, randomized (R), double blind (DB), PC trial of two doses of Creon MMS in 94 adult patients with pancreatectomy (PY) or chronic pancreatitis (CP). Safety measures were collected from start of placebo period through end of 2-3 weeks of DB (Creon or placebo) treatment.
Prior Infant CF Safety Study (S245.3118)	Summary	R, OL, cross-over (CO) study of CFC and Creon MMS in 36 infants 6-36 months old. 2 weeks of CFC followed by 2 weeks of MMS, or 2 weeks of MMS followed by 2 weeks of CFC.
Prior Pediatric CF Safety Study (S245.3105)	Summary	10 week, R, OL, CO study of Creon MMS and MS in children, 3-17 years. 2 week P run-in followed by either 4 weeks of MS followed by 4 weeks of MMS, or 4 weeks of MMS followed by 4 weeks of MS.
Prior Young Adult CF Safety Study (K245.5004)	Summary	6 week. R, OL, CO study of Creon MMS and MS in 34 children, 7-31 years. 2 wk P run-in followed by either 2 weeks of MS followed 2 weeks of MMS, or 2 weeks of MMS followed by 2 weeks of MS.

This ISS review was conducted using safety datasets submitted to the CR amendment, including individual safety datasets for the New Infant CF Study and the New Adult PEI Study, and the pooled safety dataset (ADV), which contained all AEs reported in the 50 studies submitted to the ISS. For the purpose of this review, adverse events (AEs) are designated as associated with exposure to drug or placebo within fourteen days, inclusive, prior to the first report of an event. AEs occurring 15 days or more from last exposure are labeled "post-treatment".

7.1.1 Deaths

Eighteen deaths were reported in the Safety Update. Eight deaths occurred in patients who were enrolled in clinical trials described in the ISS. Reports of the remaining ten deaths, which were not described in the ISS, were received from one of two sources: either from one of the seven studies which were not integrated into the ISS, or from non-US post-marketing reports, including compassionate use programs.

Table 8 below displays the eight deaths reported in the ISS by drug treatment group (Creon MMS, Creon MS, Other PEPS, and placebo). Deaths occurred in about 0.3% of patients receiving Creon (MMS or MS) during or within 14 days of treatment, and in about 0.3% of patients receiving placebo during or within 14 days of treatment. No deaths were reported in the ISS in 311 patients during administration of Other PEPs (not shown). This Reviewer concludes that the use of Creon MMS (CMP) is not associated with an increased risk of death as compared to placebo treatment.

Table 8: All deaths in studies reported in the ISS

Deaths, Adverse Events, and Serious Adverse Events included in the ISS	Total		Creon MMS		Creon MS		Any Creon		Placebo	
	n	%[1]	n	%	n	%	n	%	n	%
Patients in NDA Safety Update 2006	1546	100	594	100	991	100	1333	100	589	100
Number of Deaths[2]	8	0.5	1	0.2	3	0.3	4	0.3	2	0.3

[1] Percentage of patients in each treatment group who died
[2] Does not include 10 deaths from post-marketing reports

Of the eight deaths reported in the ISS, five occurred during or shortly after Creon treatment, three occurred during or shortly after placebo treatment, and no deaths were reported during administration of Other PEPs. Of ten deaths reported outside the ISS, all deaths occurred during treatment with Creon, and no deaths were reported during treatment with placebo or Other PEPs.

In the 14 of 18 cases where cause of death could be determined, death appeared to be directly or indirectly attributable to underlying disease. In the three placebo-treated patients who died, one patient's cause of death was not reported, one died of cardiopulmonary decompensation, and one died of cardiovascular failure. In the 15 Creon-treated patients who died, two patients' cause of death was not reported, five patients died of cancer (i.e., metastasis of pre-existing carcinoma), four patients died of cardiopulmonary complications (e.g., due to infection, respiratory failure, and/or complications of CF), two patients died of cardiovascular failure, and one patient each died of ruptured aortic aneurysm, liver failure (due to pancreatic carcinoma), and subdural hematoma. These findings are summarized in Table 9 below. Narrative descriptions of all eighteen deaths are located in Appendix section 10.1.3 of this review.

Table 9: All Deaths Reported In The Complete Response

Study/Patient/ Treatment	Study Description	Cause of Death	Other Clinical Findings	Reviewer's Conclusion
Deaths Reported in Studies Included in the ISS				
223.8.01 Patient 111 11 year old boy; Creon	5-week, OL, CO study of 2 Creon MS preparations in CF	Cardiopulmonary arrest	History of pulmonary complications, methicillin resistant staphylococcus aureus, and depression. Recent fever, chest pain, productive cough and shortness of breath.	Death attributable to complications of underlying disease. Relation to drug unlikely
Creo.630 Patient 7 71 year old man; Creon	R, DB, PC, Creon MS vs. Placebo, Malnutrition in Elderly, No PEI.	Not stated	Parkinsonism and recent onset of urinary tract infection, dehydration, and altered sensorium.	Cause of death not determined from information provided. Relation to drug unknown.
Patient 10 89 year old woman; Creon	See above	Acute cardiac decompensation	History of cardiac insufficiency and atrial fibrillation.	Death due to complications of underlying disease. Relation to drug unlikely
Patient 30 89 year old woman; Creon	See above	Ruptured aortic aneurysm	History of phlebitis and perforated ulcer. Rupture of a previously undiagnosed aortic aneurysm	Death due to complications of an underlying disorder. Relation to drug unlikely
Patient 5 89 year old woman; Placebo	See above	Cardio-pulmonary decompensation	History of angina and asthma Hospitalized with bronchial infection.	Death due to complications of an underlying disorder. Relation to placebo unlikely
Patient 11 87 year old woman; Placebo	See above	Not stated	History of hypertension and "arteriopathy". History of broncho-pulmonary infection, melena, acute anemia, dehydration, and coma.	Cause of death not determined from information provided. Relation to placebo unlikely
Creo.631 Patient 39 77 year old man; Placebo	R, DB, PC, Creon MS vs Placebo. Malnutrition in Elderly, No PEI.	Cardiovascular failure	Carotid and coronary vascular disease, who developed cardiovascular failure.	Death due to complications of an underlying disorder. Relation to placebo unlikely
S245.3.117 Patient 1-C-1 21 year old man; Creon	OL, non-fixed dose of Creon MMS in CF	Not stated	History of pulmonary symptoms related to cystic fibrosis. Cough, respiratory failure, and renal failure developed while on treatment Death due to circulatory failure.	Death due to underling disease. Relation to drug unlikely

Table 9: All Deaths Reported In The Complete Response

Study/Patient/ Treatment	Study Description	Cause of Death	Other Clinical Findings	Reviewer's Conclusion
Deaths In Studies Not Integrated into the ISS or from Non-US Post-Marketing Report				
245.3.103 Patient 2102-L-01 66 year old woman; Creon MMS	Compassionate use program	Metastatic primary carcinoma	History of pancreatectomy due to pre-existing carcinoma of the gall bladder	Death due to underling disease. Relation to drug unlikely
Patient 2170-L-01 55 year old man; Creon	Compassionate use program	Metastatic primary carcinoma	History of pancreatectomy due to pre-existing pancreatic carcinoma	Death due to underling disease. Relation to drug unlikely
Study S245.4.007 Patient 208 85 year old woman; Creon	Protocol not provided	Recurrent primary carcinoma	History of hypertension, Parkinson's, gastric cancer, and pneumonia	Death due to underling disease. Relation to drug unlikely
Patient 403 75 year old woman; Creon	Protocol not provided	Recurrent primary carcinoma	History of pre-existing peritoneal carcinosis	Death due to underling disease. Relation to drug unlikely
Protocol Laugier Patient 22 Age and gender not reported; Creon MS	Protocol not available	Not provided	History of chronic pancreatitis, cardiomyopathy, and positive HIV serology	Cause of death not provided. Relation to drug unknown
Patient 21 38 year old, gender not reported; Creon MS	Protocol not available	Pancreatic Cancer	History of chronic pancreatitis and hypertrophy of the pancreatic head	Death due to underlying disease. Relation to drug unlikely
Study 245.3.104 Patient 2032-O-04 52 year old man: Creon MMS	Protocol not stated	Liver failure due to pre-existing carcinoma	History of pancreatic carcinoma	Death due to underlying disease. Relation to drug unlikely
Patient 1030-C-01 9 year old boy; Creon	Compassionate use not associated with study	Respiratory failure	CF with antecedent pulmonary disease	Death due to underlying disease. Relation to drug unlikely
Patient 2200-C-01 10 year old girl; Creon		Respiratory failure	CF with antecedent pulmonary disease	Death due to underlying disease. Relation to drug unlikely
Patient 2140-L-02 70 year old man; Creon		Subdural hematoma secondary to fall	History of chronic pancreatitis	Death due to trauma. Relation of death to drug unlikely, and relation of fall to drug unknown.

In summary, all of the deaths reported in the ISS appear to be attributable to underlying disease or documented co-morbidities, and there is no indication from these results that treatment with Creon MMS (CMP) is associated with an increased risk of death. No deaths were reported in children less than 18 years old.

7.1.2 Other Serious Adverse Events

This section begins with a brief discussion of the methodological issues related to the safety assessment of patients treated with Other PEPs, followed by reviews of SAEs from the New Infant CF Study, the New Adult PEI Study, and a description of SAEs from the entire ISS. Because of the lack of safety information in children seven years and younger noted in the review of the original NDA, this Reviewer also assessed the types and frequencies of SAEs in the three studies included in the ISS that enrolled infants, children, and young adults with CF (i.e., Prior Infant Safety Study, the Prior Pediatric Safety Study, and Prior Young Adult CF Study).

A direct comparison of safety between Creon MMS and Other PEPs cannot be made for the following reasons: 1) For the 311 patients treated with Other PEPs, only 21 patients participated in the only study reported in the ISS with Creon MMS, Other PEPs, and placebo treatment arms; 2) The ten remaining studies with Other PEP treatment arms (N=290 patients exposed to Other PEPs) did not have a Creon MMS or placebo treatment arm, or a non-treatment Baseline phase; 3) Half of the 311 patients treated with Other PEPs participated in studies where assessment of seriousness and severity of AEs were not done. Therefore, no conclusions can be drawn for comparisons of safety (SAE or non-serious AE) between Creon MMS and Other PEPs, and between Other PEPS and placebo.

7.1.2.1 Serious Adverse Events Reported in the New Infant CF and New Adult PEI Studies

The New Infant CF study included a one-week, open-label, placebo run-in period, and an eight-week, open-label, Creon MMS treatment period in 12 infants with cystic fibrosis, ages one to 24 months. Safety data were collected from the beginning of the placebo period through the eighth week of Creon treatment. No treatment period SAEs were reported, and no deaths were reported.

The New Adult PEI study was a two- to three-week trial of Creon MMS in 94 adult patients with PEI due to chronic pancreatitis (CP) and pancreatectomy (PY). The study began with a one-week single-blind placebo run-in period, followed by a one-week, double-blind Creon MMS treatment period. On completion of the placebo run-in period, patients received seven days of treatment with either placebo, low-dose (1.5 gram/day) Creon (60,000 lipase U/day), or high-dose (3.0 gram/day; 120,000 lipase U/day) Creon. Safety data were collected from the beginning of the placebo run-in phase through the end of the double-blind treatment period.

Three patients experienced SAEs during the single-blind placebo run-in phase, which included hypoglycemia (2 patients), and edema (1). SAEs during the single-blind phase were more common in the placebo group (10%) compared to the low-dose (0%) and high-dose Creon groups (3%). Four patients experienced SAEs during the DB treatment phase. Three patients in the placebo group experienced one SAE each, including pyrexia, subdural hematoma, and hypoglycemia. One patient in the high-dose Creon group experienced pyrexia. No SAE was assessed as being related to study drug, and no SAE resulted in a patient discontinuing from the study. These findings are summarized in Table 10 below which displays incidence rates of AEs, SAEs, and deaths by treatment group.

Table 10: New Adult PEI Study; Summary Incidence of AEs and Deaths during Double-Blind Treatment

Event	Placebo (N=30)			Low-Dose (N=31)			High-Dose (N=33)		
	Events	N	%	Events	N	%	Events	N	%
Any AE	54	19	63	41	23	74	63	23	70
SAE	3	3	10	0	0	0	1	1	3
Deaths	0	0	0	0	0	0	0	0	0

N= number of patients in each study arm.

Thus, in the New Adult PEI Study, treatment with Creon did not appear to be associated with an increased incidence of SAEs in adult patients with PEI as compared to placebo, or by comparison of the high-dose group to the low-dose group, although it is noted that the number of patients treated in this short-term study was small. Although the New Infant Study lacked a control, there were no SAEs reported during this short-term study, and no indication of an SAE safety signal with Creon treatment in these patients.

7.1.2.2 Serious Adverse Events Reported in the ISS

In general on review of the ISS, the types and frequencies of SAEs reported in the Creon-treated patients are similar to SAEs reported in placebo-treated patients, and are similar to those SAEs previously reported in other reviews of Creon and in the existing experience with this product. These findings are generally similar to, and not readily distinguishable from, AEs due to underlying primary disease or are commonly reported complications of primary disease (such as infectious and respiratory complications of CF).

Overall, for all SAEs reported in the ISS, SAEs were reported in 3% of patients receiving Creon MMS, 5% of patients receiving Creon MS, 3% of patients receiving placebo, and 1% of patients receiving Other PEPs. The most commonly reported SAEs by System Organ Class (SOC) across all treatment groups (Creon MMS, Creon MS, Other PEPs, and placebo) were gastrointestinal disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders. The rates of the most commonly reported SAEs by Preferred Term (PT) in the Creon MMS group were pyrexia (0.7%) cough (0.5%), and acute bronchitis (0.3%). The most common SAEs in the placebo group were superinfection of the lung and hypoglycemia (each in 0.5%). Differences noted between the Creon MMS and placebo-treated groups were minor and likely related to underlying diagnoses (e.g. diabetes mellitus). Table 11 below displays SAEs reported in the ISS which occurred in one or more patients treated with Creon MMS, Creon MS, Other PEPs, or Placebo.

Table 11: SAEs occurring in ≥1 patients in Entire ISS Population

SAEs Occurring in ≥ 1 patients											
		Total (N=1,546)		MMS (N=594)		MS (N=991)		Other PEP[1] (N=311)		Placebo (N=589)	
		N	%	N	%	N	%	N	%	N	%
Total SAEs		95	6.1	20	3.4	48	4.8	5	1.3	21	3.4
SOC	**Preferred Term**										
Gastrointestinal	Abdominal pain	7	0.4	1	0.2	5	0.5	0	0	1	0.2
	Vomiting	4	0.3	1	0.2	3	0.3	0	0	0	0
	Nausea	3	0.2	0	0	3	0.3	0	0	0	0
General and administration site	Pyrexia	7	0.5	4	0.7	2	0.2	0	0	1	0.2
Infections and infestations	Bronchitis acute	3	0.2	2	0.3	1	0.1	0	0	0	0
	Pneumonia	8	0.5	1	0.2	6	0.6	0	0	0	0
	Superinfection lung	3	0.2	0	0	0	0	0	0	3	0.5
	Upper respiratory tract infection	1	0.1	0	0	0	0	0	0	0	0
Metabolism and nutrition	Hypoglycemia	5	0.3	0	0	2	0.2	0	0	3	0.5
	Dehydration	3	0.2	0	0	3	0.3	0	0	0	0
Respiratory, thoracic and mediastinal	Cough	3	0.2	3	0.5	0	0	0	0	0	0
	Lung disorder	8	0.5	1	0.2	7	0.7	0	0	0	0
Skin and subcutaneous tissue	Cold sweat	1	0.1	0	0	0	0	0	0	1	0.2

[1] Including Cotazym, Pancrease, Pancrex, and Panzytrat commercial PEPs

Additional analyses of SAEs by this Reviewer by Baseline demographic characteristics for patients in the ISS showed that for patients with CF, male and female patients were approximately equally represented. In the chronic pancreatitis (CP), acute pancreatitis (AP), and pancreatectomy (PY) populations, male to female ratios were about 2 to 1. For CF patients, male and female patients reported any SAE about as frequently. For patients with CP, AP and PY, males as compared to females reported any SAEs in a ratio of approximately 2:1, which reflected gender composition at entry. Thus, no differences by gender were seen in rates of SAE reporting with Creon exposure. There was also no obvious association in rates of SAE reporting by Baseline demographics for race (data not shown).

Thus, this Reviewer concludes that the type and incidence of SAEs reported in the Creon MMS and placebo treatment groups in the ISS are similar.

7.1.2.3 Serious Adverse Events: Pediatric Experience

This Reviewer also assessed the SAE experience of the pediatric sub-population by reviewing adverse event information from the three pediatric CF safety studies, including the Prior Infant CF Safety, Prior Pediatric CF Safety Study, and Prior Young Adult CF Safety Study. It is noted that the AE dataset did distinguish between CFC and MMS treated patients, and SAEs in CFC and MMS treated patients are reported as occurring in MMS treated patients in this discussion and in table 11 below.

SAEs were more commonly reported in pediatric patients treated with Creon MMS (9 of 130 patients; 7%) than patients treated with placebo (2 of 40 patients; 3%). The relevance of this finding is unclear, but may be explained by a greater exposure time of patients to Creon MMS (about 524 patient weeks of exposure) than to placebo (about 60 patient weeks of exposure). The most commonly reported SAEs by SOC overall for all of these pediatric patients were gastrointestinal disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders. By Preferred Term, only lower respiratory tract infection was reported by more than one patient (reported by two patients). These finding findings are summarized in Table 12 as follows.

Table 12: SAEs in the Prior Infant CF Safety Study, Prior Pediatric CF Safety Study, and Prior Young Adult CF Safety Study

Exposure in three Pediatric CF Studies		Total (N=133)		MMS (N=130)		MS (N=93)		Placebo (N=40)	
		N	%	N	%	N	%	N	%
		12	9	9	7	2	2	1	2.5
SOC	Preferred Term								
Gastrointestinal	Abdominal pain upper	1	0.8	0	0	1	0.7	0	0
	Distal intestinal obstruction syndrome	1	0.8	1	0.8	0	0	0	0
	Intussusception	1	0.8	1	0.8	0	0	0	0
	Meconium ileus	1	0.8	1	0.8	0	0	0	0
Infections and infestations	Appendiceal abscess	1	0.8	1	0.8	0	0	0	0
	Acute otitis media	0	0	0	0	0	0	1	2.5
	Lower respiratory tract infection	2	1.6	2	1.6	0	0	0	0
	Lung infection pseudomonal	1	0.8	1	0.8	0	0	0	0
Reproductive system and breast	Testicular torsion	1	0.8	1	0.8	0	0	0	0
Respiratory, thoracic and mediastinal	Bronchial obstruction	1	0.8	1	0.8	0	0	0	0
	Bronchospasm	1	0.8	0	0	1	0.7	0	0
Surgical and medical procedures	Gastrostomy tube insertion	1	0.8	1	0.8	0	0	0	0

Six of 34 patients in study Prior Young Adult CF Safety Study were $\geq$ 18 years of age.

The incidence of SAEs in the pediatric safety studies for patients treated with Creon MMS (7%) is about twice as high as the incidence in placebo-treated patients (3%). The relevance of this finding is unclear, but may be explained by a greater exposure time of patients to Creon MMS (about 524 patient-weeks of exposure) than to placebo (about 60 patient-weeks of exposure). The lower incidence of lower respiratory tract infections in the placebo-treated as compared to Creon MMS-treated patients may also be due to the shorter duration of placebo treatment, and the lower number of placebo treated patients compared to Creon MMS (CMP) treated patients.

In summary, from the results reported in these three studies, SAEs in children with CF treated with Creon MMS are similar in type to SAEs reported in the overall Creon MMS-treated population included in the ISS. The most commonly reported SAEs were gastrointestinal disorders and upper and lower respiratory tract infections, and appear to be consistent with underlying disease. Differences in

incidence rates for SAEs between the Creon MMS-treated and placebo-treated patients were likely attributable to the longer duration of exposure to Creon MMS than to placebo in these studies.

7.1.2.4 Summary Discussion of SAEs

The Serious Adverse Events reported in the ISS were predominantly reported in the System Organ Class categories of (1) general disorders and administration site conditions, (2) gastrointestinal disorders, (3) infections and infestations, and (4) respiratory, thoracic and mediastinal disorders. The most commonly reported SAEs by PT in the Creon MMS group were pyrexia (0.7%), cough (0.5%), and acute bronchitis (0.3%), and the most commonly reported SAEs in the placebo group were superinfection of the lung and hypoglycemia (each in 0.5%). In the opinion of this Reviewer, differences noted between the Creon MMS-treated and placebo-treated groups were minor, and were likely related to underlying diagnoses (e.g. diabetes mellitus).

Thus, in general, the types and frequencies of the reported SAEs in Creon MMS-treated patients are similar to those reported in the placebo-treated patients, and to those SAEs reported during the original NDA review of this product. These findings are generally similar to, and not readily distinguishable from, underlying primary disease or common complications of primary disease.

No SAEs were reported in the New Infant CF Study.

The most commonly reported SAEs (by SOc and PT) from the Prior Infant Safety Study, the Prior Pediatric Safety Study, and Prior Young Adult CF Study (gastrointestinal and respiratory) are similar to the most commonly SAEs reported in the overall ISS population treated with Creon MMS (CMP). In the opinion of this Reviewer, the increased incidence of SAEs in children treated with Creon MMS in the Prior Infant Safety Study, the Prior Pediatric Safety Study, and Prior Young Adult CF Study (7%) compared to all patients in the ISS treated with Creon MMS (CMP) (3%) is not clinically meaningful due to lack of consistent study methods and treatment protocols. This Reviewer concludes that the similarity in types of SAEs reported by Pediatric and Adult is more relevant.

In the New Adult PEI study, three patients experienced SAEs in the placebo run-in phase. Of four patients with SAEs during the DB treatment phase, three patients in the placebo group experienced one SAE each, including pyrexia, subdural hematoma, and hypoglycemia. One patient in the high-dose (3 gram/day) group had pyrexia. No SAEs were attributable to administration of Creon MMS. This Reviewer concludes that SAEs in patients in this study are substantially similar in type to SAEs reported in the ISS.

Thus overall, this Reviewer concludes that in the ISS, in the studies individually reviewed (New Infant CF and Adult PEI studies), and in the pooled assessment of the Pediatric Safety Study experience, the types of SAEs reported appear to be related to entry diagnoses, such as CF, PY, or cancer, or are age-related, such as occult cardiovascular disease in the elderly, and do not appear to be directly attributable to the use of Creon MMS. This Reviewer also concludes that there is no clinically meaningful difference in the types of SAEs reported in children with CF treated with Creon MMS

(CMP) compared to adults with CF treated with Creon MMS or for the entire ISS population treated with Creon MMS (CMP).

7.1.3 Dropouts and Other Significant Adverse Events

Information on patients who withdrew (dropouts) from the studies included in the ISS is followed by data on dropouts from the non-integrated, long-term studies. This Reviewer designated all AEs reported on the day of withdrawal and the reason stated in the accompanying CRF (if available for review) as being temporally associated with the withdrawal. If the reason for withdrawal was not provided in the CRF, if the CRF was not available for review, or if no AE was listed in the AE dataset on the day of withdrawal, AEs listed on the most recent preceding day are designated as being temporally associated with the withdrawal.

7.1.3.1 Profile of Dropouts in the ISS

Throughout all drug phases, including pre-treatment and post-treatment, of 1,546 patients treated with any Creon product, any Other PEP, or placebo, 53 patients (3%) withdrew due to 100 listed AEs. These withdrawals appeared to be evenly distributed across the treatment groups, including 2% of all patients treated with MMS, 2% treated with MS, and 3% treated with Placebo w.0ithdrawing due to AEs. No withdrawals were reported in patients receiving Other PEPs, but as discussed (in the introduction to section 7.1.2 above), methodological issues in studies of Other PEPs prevented a complete assessment of the safety of the Other PEPs.

Withdrawal due to an AE was more common in patients with acute pancreatitis (7% of 77 patients) and in patients with "other diagnoses" (9% of 106 patients), than in patients with CP (3% of 358 patients), CF (2% of 743 patients), post-pancreatic surgery (3% of 153 patients), diabetes mellitus (2% of 109 patients), and HIV (N=1, denominator unavailable). This Reviewer believes the increased incidence of withdrawal in patients with acute pancreatitis compared to withdrawals in patients with CF, CP, and post-pancreatic surgery may be explained by the frequently rapid change in the clinical state of patients with acute pancreatitis compared to patients with chronic pancreatitis and cystic fibrosis.

One additional demographic trend noted by this Reviewer was that in patients who withdrew due to AEs, almost all (98%) of the 53 patients who withdrew were Caucasian, whereas of the entire ISS population, 67% of was Caucasian, 21% was of Unknown race, 4% was of Other race, 7% was Asian, and 2% was Black. There was no obvious explanation for this imbalance, but it is unlikely to be clinically relevant.

No trends by gender were seen for patient withdrawals.

7.1.3.2 Adverse Events Associated with Dropouts

The most commonly reported AEs leading to withdrawal were abdominal pain, diarrhea, nausea, and vomiting (reported by 1% of patients in the ISS, each). The most commonly reported AEs leading to withdrawal in patients treated with Creon MMS were abdominal pain, diarrhea, and nausea (1% each). The most commonly reported AE associated with withdrawal in patients treated with placebo was superinfection of the lung (reported by 2 patients, <1%); the remainder of AEs associated with withdrawal in the placebo-treated group were reported by one patient each. In the opinion of this Reviewer, AEs leading to withdrawal are related to underlying diagnoses, and the differences in AEs leading to withdrawal in the placebo and Creon MMS (CMP) treated groups is not clinically meaningful.

The most commonly reported (by ≥2 patients) AEs leading to withdrawal are summarized in Table 13 below (a table of all AEs leading to withdrawal is located Appendix 10.2 of this review). The table does not include information on three patients who withdrew after screening but before first study dose (placebo or study drug), and does not include AEs which were causally related to death, which are described in section 7.1 of this document.

Table 13: AEs Leading to Withdrawal occurring in ≥2 patients in the ISS

All Patients who dropped out by treatment group		All Patients (N=1,546)		MMS (N=594)		MS (N=991)		Placebo (N=589)	
		N	%	N	%	N	%	N	%
		53	3.4	14	2.4	19	1.9	17	2.9
Listing of Individual AEs									
SOC	Preferred Term	N	%	N	%	N	%	N	%
Cardiac disorders	Cardiac failure	2	0.1	0	0	1	0.1	1	0.2
Gastrointestinal disorders	Abdominal pain	10	0.7	6	1	3	0.3	1	0.2
	Diarrhea	7	0.5	4	0.7	2	0.2	1	0.2
	Nausea	7	0.5	3	0.5	4	0.4	0	0
	Vomiting	7	0.5	2	0.3	4	0.4	1	0.2
	Abdominal pain upper	3	0.2	0	0.0	2	0.2	1	0.2
	Constipation	2	0.1	1	0.2	1	0.1	0	0
	Flatulence	2	0.1	2	0.3	0	0.0	0	0
Infections and infestations	Superinfection lung	2	0.1	0	0	0	0	2	0.3
Metabolism and nutrition disorders	Dehydration	3	0.2	0	0	3	0.3	0	0
	Hypoglycemia	2	0.1	0	0	1	0.1	1	0.2
Musculoskeletal and connective tissue disorders	Muscle spasms	2	0.1	2	0.3	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Cough	2	0.1	2	0.3	0	0	0	0
	Respiratory failure	2	0.1	1	0.2	0	0	1	0.2

In summary, withdrawal due to AEs was most commonly due to gastrointestinal complaints, and was associated with the entry diagnosis of acute pancreatitis, which possibly reflected the natural disease course of these patients. Rates of withdrawal in patients with CF, CP, and diabetes mellitus was approximately equal (2%, 3%, and 2%, respectively, of patients who withdrew had these conditions). Withdrawals were approximately evenly distributed among patients treated with Creon MMS, Creon MS, and placebo. Therefore, this Reviewer concludes that withdrawals due to AEs were most likely

related to underlying disease, and not to treatment, since patients treated with Creon MMS were no more likely to withdraw from treatment due to AEs than were patients treated with placebo.

7.1.3.3 Other significant adverse events

Rare cases of fibrosing colonopathy (FC) have been reported with PEP use, and are thought to be associated with high-dose PEP administration in younger patients. Given the severity of this diagnosis, surveillance for FC in PEP clinical development programs is relevant to the assessment of safety in this class of medications. No instances of fibrosing colonopathy (FC) were reported in the Creon ISS; however, limitations in the safety surveillance program were noted, and conclusive statements regarding the adequacy of FC case detection are not possible for several reasons. First, FC is a histopathologic diagnosis and routine surveillance with colonoscopy and biopsy was not routinely performed in any study. Second, while FC is commonly described as a symptomatically severe and acute process, literature suggests it may have a chronic indolent course; therefore, though severely symptomatic cases might have come to clinical attention during safety assessments, incipient cases might not have been recognized. Third, though fibrosing colonopathy is classically described following high-dose lipase treatment, the doses of Creon MMS administered in the New Infant CF Study, New Adult PEI Study, Prior Pediatric and Adult CF Studies, and the Prior Adult CP Study (e.g., the efficacy trials) were within current guidelines promulgated to decrease the risk of FC. Fourth, though the time of exposure required to develop FC is undetermined, the short duration of most of the studies (two to six weeks) may not have provided a long enough exposure to precipitate FC. Finally, cases of FC in the medical literature appear to have been reported only sporadically. The population studied was relatively small and given the rarity of FC, may not have been large enough to detect an FC safety signal. Therefore, this Reviewer believes that although there were no obvious cases of FC reported in this CR amendment, no conclusions can be drawn regarding the adequacy of FC case detection for the overall ISS population, and monitoring for FC is likely best performed in the post-marketing setting.

Since Creon is an animal-derived protein product, allergy/hypersensitivity reactions are of interest for the assessment of safety of Creon administration. No cases of anaphylaxis were reported in the ISS; however, eleven hypersensitivity events were reported in five patients. The verbatim terms used for the two patients receiving Creon MMS were allergy and allergies (itching of eyes/sneezing). The investigator term used for the one patient receiving Creon MS was allergic reaction. The investigator terms used for the two patients receiving placebo were environmental allergies and allergy. None of the patients withdrew or died due to these events, and only two of the eleven events required treatment. These findings are not unexpected because PEPs act locally in the gut and systemic absorption is minimal, decreasing the likelihood of systemic reactions such as anaphylaxis. The similar rates of hypersensitivity reactions in the Creon MMS and placebo group, and the similar descriptions provided suggest these events were related to environmental allergies. In the opinion of this Reviewer, monitoring for anaphylaxis was felt to be adequate and treatment with Creon MMS (CMP) does not appear to be associated with a high risk of anaphylaxis or other allergic reactions.

Hyperuricemia is associated with the use of all PEPs, and is thought to be related to the purine content of pancreatic extracts from which the PEPs are produced.[4] Thus, monitoring of uric acid levels in the

Creon clinical development program was also felt to be of importance to the overall assessment of safety. Assessment of blood uric acid levels was hampered by a lack of standardized laboratory evaluations across all studies, use of differing units of measure and incorrect units of measure, and frequent errors in transcription of numerical results. Despite these limitations, the following are noted:

- None of the four patients with hyperuricemia events listed in the ISS AE dataset were receiving Creon MMS.
- Uric acid was not assessed in the New Infant CF study.
- Uric acid was assessed in the New Adult PEI study. There was no effect of Creon treatment on blood uric acid noted in this study.
- Uric acid was assessed in the Prior Pediatric CF study. Hyperuricosuria was noted in 5% (2 of 34) patients during treatment with Creon MMS. Both patients had baseline blood uric acid levels near the upper limit of normal. One patient's blood uric acid increased by 1 mg/dL and the other patient's blood uric acid increased by 0.6 mg/dL. The dataset does not indicate if any clinical action was taken. In the 50% of patients randomized to placebo withdrawal, there was no trend toward decrease in blood uric acid when switching from Creon MMS to placebo. The individual study report is not available for review.
- Uric acid was assessed in the Prior Adult CF Study. Hyperuricosuria was seen in 16% (5 of 31) patients treated with Creon MMS. All five patients had baseline blood uric acid levels near the upper limit of normal. One patient's blood uric acid level increase from 3.8 to 7 mg/dL on randomized withdrawal. The dataset does not indicate if any clinical action was taken. In the 50% of patients randomized to placebo withdrawal, there was no trend toward a decrease in blood uric acid when switching from Creon MMS to placebo. The individual study report is not available for review.

In the opinion of this Reviewer, hyperuricemia was associated with Creon MMS treatment in clinical studies. This finding is relevant to patients with the impaired liver function commonly seen in older patients with cystic fibrosis and in patients with chronic pancreatitis. This finding is also relevant in patients with impaired renal function, and impaired uric acid metabolism (e.g. gout). Should Creon receive NDA approval, labeling should address the risk of hyperuricemia associated with Creon administration.

7.1.4 Other Search Strategies

No other search strategies were performed.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse event (AE) collection methods varied between studies and included onsite interviews, review of patient or caregiver diaries, physical examination of the patient, radiological and other procedural test information, and review of clinical laboratory data. AEs were monitored and recorded by

investigators or their designees from the time of study entry (signing of the Informed Consent) and at each study visit through the completion of the studies. Clinically significant worsening from screening in physical examinations, vital signs, and laboratory evaluations were documented as AEs.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The Sponsor reported all AEs in the final ISS (ADV) dataset using Medical Dictionary for Regulatory Activities (MedDRA) SOC and PT terminology. The New Pediatric CF, Prior Pediatric CF, and Prior Adult CF studies, and the New and Prior Adult PEI studies were originally coded using MedDRA, and this Reviewer assesses that the MedDRA SOC and PT coding for these studies was appropriate. Adverse event information from the remaining studies submitted to the ISS was originally coded using either MedDRA or Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). AEs coded in COSTART were converted to MedDRA for incorporation into the ADV dataset. A direct comparison of COSTART and MedDRA terms could not be performed by this Reviewer; however, in studies where COSTART was originally used, comparison of the verbatim terms with corresponding MedDRA terms indicates that MedDRA SOC and PT terms used in ADV appeared generally appropriate.

7.1.5.3 Incidence of Common Adverse Events

This Reviewer constructed incidence rate tables of common AEs from the ISS safety dataset (ADV dataset), which included all AEs in the ISS pooled from the individual studies. AE incidence rates were calculated using all patients who received at least one dose of study medication as the denominator, with recurrent or continuing AEs counted only once. AE incidence rates for each treatment (Creon MMS, Creon MS, Other PEPs, and placebo) were calculated using all patients who received at least one dose of each treatment as the denominator. AEs occurring during the screening/baseline period were reviewed, and only notable AEs occurring during this time period are discussed.

In addition to an assessment of the AEs from all pooled studies reported in the ISS, this Reviewer also analyzed the AEs reported in individual studies, including the New Infant CF Study and the New Adult PEI study, and performed an assessment of the Pediatric CF population AE experience in the pooled AE dataset for the Prior Infant, Pediatric and Young Adult Safety Studies.

Additionally, approximately 1,200 AEs listed in the ADV dataset of the ISS were not classified for seriousness. These AEs were predominantly from studies where the seriousness and severity of AEs were not intended to be assessed. To determine if type or incidence of AEs in this group differed from type and incidence of AEs reported in the overall ISS, this Reviewer assessed type and incidence of AEs with unknown seriousness. The denominator population was empirically assigned as the denominator of the total population of all studies where at least one patient had an AE of unknown seriousness. Type and incidence of AEs of unknown seriousness conclude this section.

Assessment of Common Adverse Events

Common AEs in the Prior Infant CF Safety Study, Prior Pediatric CF Safety Study, and Prior Young Adult CF Safety Study

The assessment of the AEs in the pooled analysis of the three pediatric CF safety studies (Prior Infant, Pediatric, and Young Adult CF Safety Studies) was limited by the finding that the Sponsor did not use uniform treatments, blinding, and controls in these studies. Thus, the objective assessment of causality of the commonly reported AE was felt to be impaired.

In the pooled analysis of these three studies, AEs were reported in 61% of the 133 patients treated with Creon MMS and in 15% of the 40 patients treated with placebo. The most common AEs reported in patients treated with Creon MMS were headache (43%), cough (34%), abdominal pain (20%), and lower respiratory tract infection (17%). The most common AEs reported in patients treated with placebo were nasopharyngitis (5%), bronchitis (3%), and bronchial obstruction (35%). These AEs are similar to common complaints reported in children with CF and are similar in type to common AEs reported in the ISS in all patients treated with Creon MMS. Due to differences in study designs (e.g., two of the studies were open label) and since placebo control was only provided to 40 of 134 patients (30%), the differences in types and frequencies of AEs between the placebo and Creon MMS groups are likely not clinically meaningful, and definitive statements regarding causality cannot be made. These findings are summarized in Table 14 in section 7.1.5.4 below.

Common AEs in the New Infant CF Study
In the New Infant CF Study, three AEs were reported in two patients during the Baseline period. One patient had malnutrition and cow's milk intolerance, and one patient had meteorism. There were 21 non-serious AEs reported during treatment with Creon MMS. The most common AEs reported during Creon treatment were pyrexia (33%), cough (25%), constipation (17%), and respiratory tract infections (17%). Conjunctivitis, abdominal pain NOS, viral infection NOS, nasopharyngitis, gastroenteritis adenovirus, rhinitis NOS, and pharyngeal pain each occurred in 8% of the study population. These findings are similar to common presenting complaints in healthy infants and infants with CF. The increased incidence of AEs during double-blind treatment compared to the Baseline phase is likely due to the short Baseline period (seven to ten days) compared to the treatment period (eight weeks). This Reviewer concludes that the AE results in this study can be used in labeling to describe safety of Creon MMS (CMP) in infants with CF from one to 24 months of age.

Common AEs in the New Adult PEI Study
In the New Adult PEI study, 45 patients experienced an AE during the placebo run-in period. The most common AEs during the placebo run-in period were diarrhea (9% of patients), hypoglycemia (7%), and abdominal distension, loose stools, and abnormalities of alanine aminotransferase and aspartic acid aminotransferase (5% each). AEs during the placebo run-in period were less common in the group randomized to placebo during double-blind treatment (40% of patients in the placebo group, 52% of patients the low-dose group, and 52% of patients in the high-dose group).

During the treatment phase, 64 of 94 patients reporting at least one AE, including 63% of patients in the placebo group, 70% in the high-dose group, and 74% in the low-dose group. The lower incidence

of AEs in the group randomized to placebo during double-blind treatment is similar in magnitude to the lower rate of AEs in the placebo group noted during the single-blind placebo treatment phase. Review of the study report and case report forms (CRFs) was not helpful in determining why AEs were less common in the placebo group during the single-blind and double-blind phases.

The most common AEs reported by patients overall (placebo, low-dose Creon MMS, or high-dose Creon MMS) during the DB treatment period were abdominal pain (10%), constipation (9%), and abdominal distension, diarrhea, and malaise (7% each). The most common AEs in the placebo group were malaise (14%), abdominal pain, abdominal distension, and hypoglycemia (10% each). The most common AEs in the low-dose group were abdominal pain, back pain, and headache (10% each). The most common AEs in the high-dose group were constipation and diarrhea (15% each), followed by abdominal pain, vomiting, and gastrointestinal upset (9% each).

This Reviewer concludes that the AEs reported in the placebo and Creon treatment groups reflect underlying pathophysiology, and although some differences in types and frequencies of AEs were noted between the treatment groups, these differences were felt to be minor. In the opinion of this Reviewer, the treatment of adult patients with PEI due to PY and CP with Creon MMS does not appear to be associated with an obvious safety signal for AEs, and most AEs were intolerances noted predominantly in the Gastrointestinal system. This safety information is similar to the AE profile of Creon noted in previous studies and in the medical literature with Creon (and other PEPs), and is adequate to inform the labeling of Creon MMS (CMP) in patients with PEI due to PY and CP. These findings are summarized in Table 15 in section 7.1.5.4 of this review.

Common AEs in the ISS

This Reviewer defined AEs as events in the ADV dataset that occurred during treatment (drug or placebo treatment), inter-period drug holidays and run-in phases, or within 14 days of last drug or placebo dose. This analysis identified 3,766 non-serious events in 1,011 patients in the ISS safety dataset, including events of unknown seriousness. The Sponsor used a similar strategy, but used the EXTADV dataset and included events within 10 days of last dose, which yielded 3,621 non-serious events occurring in 983 patients. The greater number of patients and AEs derived with the ADV dataset is explained by including four more days of post-treatment events, all inter-period drug holiday events, and run-in phase AEs. Overall, there is no clinically meaningful differences seen between the two analyses performed (by the Sponsor and by this Reviewer), and the following results are summarized from this Reviewer's analysis of common AEs reported in the ISS.

AEs were reported in 65% of all patients included in the ISS, including in 61% of patients treated with Creon MMS, 47% of patients treated with Creon MS, 49% of patients treated with Other PEPs, and 49% of placebo-treated patients.

The most common AEs reported overall were abdominal pain (16% of all patients), headache (14%), diarrhea (9%), cough (7%), and vomiting (7%). The most common AEs reported in the placebo-treated groups were abdominal pain (9%), diarrhea and headache (8% each), and nausea and flatulence (4% each). The most common AEs reported in the Creon CMP (MMS) group were headache (12%), abdominal pain (9%), cough (8%), and diarrhea (7%). The most common adverse events reported in the Creon MS group were abdominal pain (10%), headache (9%), and cough (7%). The most common

AEs reported in the Other PEP group were abdominal pain (10% of patients) and diarrhea (7%), followed by vomiting and cough (5% each). These adverse events reflect the underlying disease processes (e.g., PEI due to CF or PY), and were similar across treatment groups. These findings are summarized in Table 16 in section 7.1.5.4 of this review.

Common AEs in the ISS where seriousness is unknown

To calculate incidence for the population of patients where seriousness was not assessed, this Reviewer defined the denominator as the total population of all studies where at least one patient had an AE of unknown seriousness. Of the population so defined, AEs occurred in 46% of all patients, 52% of patients treated with Creon MS, 59% of patients treated with Other PEPs, and 16% of patients treated with Placebo. No patients in this population were treated with Creon MMS, and there are no instances in the ADV dataset where patients treated with Creon MMS had AEs of unknown seriousness or severity.

The most common AEs of unknown seriousness were abdominal pain (14% of patients), cough (12%), diarrhea (9%), and vomiting (9%). The most common AEs of unknown seriousness in patients receiving placebo were nausea (3%), and vomiting, diarrhea, "pain not otherwise specified", and headache (2%, each). The most common AEs of unknown seriousness in patients receiving Creon MS were abdominal pain (12%), cough (13%), diarrhea (8%), and vomiting (7%). The most common AEs of unknown seriousness in patients receiving Other PEPs were abdominal pain (23%), abnormal feces (21%), diarrhea (18%), vomiting (16%), headache (13%), and cough (11%).

The types of common AEs reported in the population where seriousness of AEs was not assessed were similar to the types of AEs reported in the entire ISS population, and AEs reflect complaints related to underlying diseases. The lower incidence of AEs in patients treated with placebo cannot be readily explained; however, may be partly accounted for by differences in study designs (e.g., open-label and blinded study designs included in the analysis).

This Reviewer concludes that the lack of assessment of seriousness should not prohibit drawing conclusions on the safety of Creon MMS (CMP), because all Creon MMS treatments and 90% of placebo treatments were provided in studies where AE seriousness was evaluated. These findings are summarized in Table 57 in Appendix 10.1.5 of this review.

7.1.5.4 Common adverse event tables

Table 14 below displays AEs occurring in 3% or greater of patients in the three pooled pediatric CF safety studies (Prior Infant CF Safety Study, Prior Pediatric CF Safety Study, and Prior Young Adult CF Safety Study) discussed in section 7.1.5.3 above.

Table 14: AEs reported in ≥3% of Patients in Three Pooled Pediatric Cystic Fibrosis Studies[1]

Exposure in three Pediatric CF Studies		Total Patients (N=133)		Creon MMS (N=130)		Creon MS (N=93)		Placebo (N=40)	
		N	%	N	%	N	%	N	%
		81	61	73	55			6	15
SOC	Preferred Term								
Ear and labyrinth	Ear pain	4	3	1	1	3	3	0	0
Gastrointestinal	Abdominal pain	27	20	11	8	16	17	0	0
	Vomiting	14	11	11	8	3	3	0	0
	Abdominal pain upper	10	8	6	5	4	4	0	0
	Nausea	8	6	6	5	2	2	0	0
	Diarrhea	6	5	5	4	1	1	0	0
	Toothache	6	5	4	3	2	2	0	0
	Constipation	5	4	3	2	2	2	0	0
	Distal intestinal obstruction syndrome	4	3	3	2	1	1	0	0
General and administration site	Pyrexia	8	6	4	3	4	4	0	0
Infections and infestations	Lower respiratory tract infection	23	17	11	8	12	13	0	0
	Nasopharyngitis	13	10	5	4	6	6	2	5
	Bronchitis	6	5	5	4	0	0	1	3
Musculoskeletal and connective tissue	Arthralgia	4	3	2	2	2	2	0	0
Nervous system	Headache	57	43	17	13	40	43	0	0
Respiratory, thoracic and mediastinal	Cough	45	34	18	14	27	29	0	0
	Pharyngolaryngeal pain	5	4	0	0	5	5	0	0
	Bronchial obstruction	4	3	3	2	0	0	1	3

[1] Prior Infant CF Safety Study, Prior Pediatric CF Safety Study, and Prior Young Adult CF Safety Study

Table 15 below displays AEs occurring in 3% or greater of patients in the New Adult PEI Study, discussed in section 7.1.5.3 above.

Table 15: New Adult PEI Study, AEs reported ≥ 3% of Patients

All patients by treatment group		Total (N=94)			1.5 g/day (N=31)			3 g/day (N=33)			Placebo (N=30)		
		AEs	N	%	AE	N	%	AE	N	%	AE	N	%
		158	65	69	41	23	74	63	23	70	54	19	63
Listing of Individual AEs													
SOC	Preferred Term	AEs	N	%	AE	N	%	AE	N	%	AE	N	%
Gastrointestinal	Abdominal pain NOS	9	9	10	3	3	10	3	3	9	3	3	10
	Abdominal distension	8	7	7	3	2	7	2	2	6	3	3	10
	Constipation	8	8	9	1	1	3	5	5	15	2	2	7
	Diarrhea NOS	7	7	7	0	0	0	5	5	15	2	2	7
	Loose stools	6	6	6	2	2	7	2	2	6	2	2	7
	Vomiting NOS	4	4	4	1	1	3	3	3	9	0	0	0
	Gastrointestinal upset	3	3	3	0	0	0	3	3	9	0	0	0
General disorders and administration site conditions	Malaise	7	7	7	1	1	3	2	2	6	4	4	13
	Chest discomfort	3	3	3	0	0	0	1	1	3	2	2	7
Investigations	Blood glucose increased	6	6	6	1	1	3	3	3	9	2	2	7
	Glucose urine present	3	3	3	2	2	7	0	0	0	1	1	3
Metabolism and nutrition	Hypoglycemia NOS	4	4	4	0	0	0	1	1	3	3	3	10
Musculoskeletal and connective tissue	Back pain	4	4	4	3	3	10	1	1	3	0	0	0
Nervous system	Headache	4	4	4	3	3	10	1	1	3	0	0	0
	Dizziness	3	3	3	0	0	0	1	1	3	2	2	7
Skin and subcutaneous tissue	Cold sweat	3	3	3	0	0	0	2	2	6	1	1	3
	Pruritus	3	3	3	2	2	7	0	0	0	1	1	3

Table 16 below displays AEs occurring in 1% or greater of patients in all studies reported in the ISS, discussed in section 7.1.5.3 above. This table includes AEs reported during treatment with any drug or placebo, and events within 14 days of most recent dose. This table does not include events that were classified as pre-treatment (for example, events which occurred between obtaining informed consent, but prior to randomization, are not included).

Table 16: AEs occurring in 1% or greater of patients in ISS studies [1, 2, 3]

All AEs in ISS		Total (N=1546)		MMS (N=594)		MS (N=991)		Other PEPs (N= 311)		Placebo (N=589)	
		N	%	N	%	N	%	N	%	N	%
		1011	65	363	61	470	47	153	49	291	49
AEs in ≥ 1% of patients in any treatment group											
SOC	Preferred Term										
Blood and lymphatic system	Anemia	15	1	3	1	6	1	3	1	2	0
Gastrointestinal	Abdominal pain	241	16	54	9	102	10	32	10	53	9
	Diarrhea	143	9	39	7	39	4	21	7	44	8
	Vomiting	109	7	35	6	43	4	16	5	15	3
	Nausea	92	6	25	4	35	4	8	3	24	4
	Abdominal pain upper	65	4	21	4	22	2	8	3	14	3
	Flatulence	72	5	16	3	25	3	8	3	23	4
	Constipation	54	4	21	4	15	2	8	3	10	2
	Abnormal feces	32	2	1	0	17	2	13	4	1	0
	Dyspepsia	32	2	15	3	3	0	1	0	13	2
	Abdominal distension	38	3	9	2	11	1	6	2	12	2
General and administration site	Pyrexia	77	5	20	3	36	4	13	4	8	1
	Fatigue	29	2	12	2	6	1	3	1	8	1
	Malaise	28	2	7	1	10	1	4	1	7	1
	Pain	25	2	6	1	12	1	3	1	4	1
	Chest pain*	13	1	6	1	5	1	0	0	2	0
	Edema peripheral*	11	1	2	0	3	0	0	0	6	1
Hepatobiliary	Hepatic function abnormal	44	3	6	1	17	2	7	2	14	2
Infections and infestations	Nasopharyngitis	63	4	24	4	26	3	3	1	9	2
	Lower respiratory tract infection	32	2	9	2	20	2	3	1	0	0
	Rhinitis	34	2	8	1	17	2	6	2	3	1
	Upper respiratory tract infection	28	2	6	1	12	1	7	2	3	1
	Influenza	29	2	7	1	12	1	1	0	9	2
	Bronchitis	22	1	13	2	5	1	2	1	2	0
	Infection	16	1	2	0	12	1	2	1	0	0
Metabolism and nutrition	Hyperglycemia	41	3	9	1	17	2	4	1.3	11	2
	Anorexia	29	2	3	0	12	1	9	3	5	1
	Hypoglycemia	32	2	4	1	8	1	0	0	19	3
	Decreased appetite	18	1	7	1	8	1	1	0	2	0
	Iron deficiency	16	1	0	0	8	1	8	3	0	0

Table 16: AEs occurring in 1% or greater of patients in ISS studies [1, 2, 3]

All AEs in ISS		Total (N=1546)		MMS (N=594)		MS (N=991)		Other PEPs (N= 311)		Placebo (N=589)	
		N	%	N	%	N	%	N	%	N	%
		1011	65	363	61	470	47	153	49	291	49
AEs in ≥ 1% of patients in any treatment group											
SOC	Preferred Term										
Musculoskeletal and connective tissue	Back pain	37	2	13	2	13	1	2	1	9	2
	Arthralgia	21	1	6	1	6	1	2	1	7	1
	Pain in extremity*	11	1	3	1	1	0	0	0	7	1
	Shoulder pain*	12	1	5	1	1	0	0	0	6	1
Nervous system	Headache	208	14	72	12	91	9	8	3	36	6
	Dizziness	22	1	6	1	6	1	0	0	10	2
Psychiatric	Insomnia*	12	1	1	0	1	0	4	1	6	1
Renal and urinary	Glycosuria*	12	1	3	1	5	1	3	1	1	0
Respiratory, thoracic and mediastinal	Cough	131	9	47	8	65	7	14	5	4	1
	Pharyngolaryngeal pain	39	3	15	3	14	1	4	1	6	1
	Productive cough	22	1	7	1	11	1	3	1	1	0
	Lung disorder	38	3	11	2	13	1	10	3	3	1
Skin and subcutaneous tissue	Rash	21	1	6	1	11	1	0	0	4	1
	Pruritus	17	1	5	1	3	0	1	0	8	1

[1]AE=Non serious AEs and AEs of unknown seriousness
[2] N=Number of persons experiencing events.
[3]The table does not include six patients with seven post-treatment AEs > 14 days after last dose; includes one event each of epistaxis, cough, lung disorder, headache, hypoglycemia, nasopharyngitis, and anemia.
* AE ≥ 1% in subgroup

7.1.5.5 Identifying common and drug-related adverse events

The method for determining AEs, SAEs, withdrawals, and deaths has been delineated in sections 7.1 through 7.1.5.3 of this review.

Hyperuricemia has been reported in patients taking PEPs[4]. The assessment of hyperuricemia is discussed in section 7.1.3.3 of this review.

7.1.5.6 Additional analyses and explorations

Since pediatric patients with CF are an important treatment population for the PEPs, this Reviewer performed additional analyses to assess the safety of Creon administration to pediatric CF patients. The analyses performed and the results of these analyses are discussed in Sections 7.1, 7.1.2.3, 7.1.2.4, and 7.1.5.3 of this review.

7.1.6 Less Common Adverse Events

Anaphylaxis and allergic/hypersensitivity reactions are discussed in Section 7.1.3.3 of this review.

Fibrosing colonopathy (FC) has been reported in patients taking PEPs, and is thought to be related to high or inappropriate dosing of PEPS, especially in young children. Reports of FC in the literature have been noted to decrease since the publication of dosing guidelines in the 1990's.[6] No cases of FC were reported in the ISS safety update. Assessment of the safety database for FC is discussed in section 7.1.3.3 of this review.

Distal intestinal outlet obstructive syndrome (DIOS) and bowel obstruction are reported in children and adults with CF. Intestinal obstruction was reported in two children with CF in the ISS, neither of whom received Creon MMS. Thus, no relationship of these two events to Creon MMS can be construed since neither patient received the drug.

No other notable less common Adverse Events were noted in the review of the safety dataset submitted in the CR amendment.

7.1.7 Laboratory Findings

All of the clinical studies included in the ISS had the collection and evaluation of laboratory data as part of their protocols. Testing procedures for biochemical, hematological, and urinary parameters varied by individual study protocol. Clinically significant laboratory abnormalities that qualified as AEs are included in the AE datasets and are reported in AE tables.

The laboratory data from studies the New Infant CF Study and the New Adult PEI study were reviewed in depth. The findings by this Reviewer and the Sponsor were identical. Pertinent positive and negative findings are presented below (please also refer to the individual study reports in appendices 10.1.1 and 10.1.2 for full descriptions).

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<u>New Infant CF Study</u>

As expected, decreased concentrations of vitamins A and E were noted at Baseline. There was a slight increase in mean values of vitamins A and E during the study, but mean values remained either below normal or at the lower range of normal for these two analytes. However, clinically meaningful decreases in vitamin E levels were seen in two patients. Marked improvement in vitamins A and E would not be expected due to the short duration of the study.

Also, mean serum cholesterol increased by 0.27 millimol/L, which may be expected with increased lipid absorption with treatment and attendant increase in cholesterol biosynthesis. There were no other notable laboratory findings.

<u>New Adult PEI Study</u>
Notable laboratory findings include:

Clinically meaningful laboratory findings were limited to hyper- or hypoglycemia, and 10 of 11 of the patients with hyper- or hypoglycemia had pre-existing diabetes mellitus. No association with Creon MMS (CMP) treatment was suspected. No other clinically meaningful trends were seen in any other laboratory parameters within or between treatment groups.

Laboratory Findings in the ISS

This Reviewer attempted to assess the potential effect of Creon MMS on blood uric acid; however, several issues hampered review including inconsistent use of units of measure, multiple errors in the dataset (e.g. physiologically impossible uric acid values), lack of uniform laboratory screening procedures, and incomplete drug or placebo treatment information at the time of laboratory assessments.

Assignation of drug or placebo treatment at time of laboratory analysis was performed by this Reviewer by matching protocol name, unique patient identifier, and date from laboratory dataset with the corresponding information in the medication dosing (MEDDOS) dataset.

Blood uric acid levels were recorded for 1,217 patients in 36 studies. There were 279 instances where apparently non-physiologic uric acid levels were due to a conversion errors between micromol/L and millimol/L. This presumed error was corrected and all values were converted to conventional units (mg/dL) for ease of review. While there were no meaningful differences between the Creon MMS and placebo groups at Baseline or during treatment, these findings may not be valid due to the limitations described above. The overall findings of the mean blood uric acid levels by treatment group at Baseline and during treatment are summarized in Table 17 below.

Table 17: Blood uric acid level in 1,009 patients with non-treatment (e.g., Baseline) and phase 1 (drug or placebo) blood uric acid values

N=1,009 [1]	**Creon MMS** N=352			**Creon MS** N=316			**Other PEP** N=65			**Placebo** N=276		
	BSL[2]	Treat[3]	Change	BSL	Treat	Change	BSL	Treat	Change	BSL	Treat	Change
Mean	4.5	4.8	0.3	4.6	4.7	0.1	4.4	4.4	0	4.3	4.5	0.2
SD	1.5	1.4	0.9	1.5	1.4	1.0	1.4	1.4	1.2	1.4	1.2	0.9

[1] Total patients with baseline and phase 1 blood uric acid values=1009
[2] Baseline blood uric acid level
[3] Treatment period blood uric acid level
Total patients with uric acid values measured one or more times=1217 (not shown)

Because patients with PEI due to CF and CP frequently have concomitant alterations in liver function, a review of laboratory abnormalities reported in the ADV AE dataset for alterations in aspartic acid and alanine aminotransferases was performed, which did not reveal any clinically meaningful differences in these analytes between patients treated with Creon MMS (CMP) and patients treated with placebo. No other noteworthy trends in laboratory findings were reported by the Sponsor or noted by this Reviewer.

7.1.8 Vital Signs

Vital signs assessments were performed according to individual study schedules. Clinically significant worsening of vital signs were documented as AEs and were considered in the overall AE assessment above. No notable, relevant, or remarkable trends in vital signs were seen.

Vital signs for the New Infant CF and New Adult PEI studies were thoroughly reviewed by this Reviewer. In the New Infant CF study, except for fevers recorded as AEs, there were no notable abnormal findings. In the New Adult PEI study, there were no clinically meaningful trends in vital signs seen within or between treatment groups compared to Baseline.

7.1.9 Electrocardiograms (ECGs)

Creon is not systemically absorbed and electrocardiogram evaluation was not part of the Creon clinical development program.

7.1.10 Immunogenicity

Creon and other porcine-derived PEPs are not systemically absorbed, and immunogenicity testing was not performed as part of the Creon clinical development program (e.g., anti-enzyme serum immunoglobulin measurements for individual components of Creon, such as lipase, were not assessed).

7.1.11 Human Carcinogenicity

Creon and other porcine-derived PEPs are not systemically absorbed and human carcinogenicity studies were not part of the Creon clinical development program, and no non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA.

A separate O-phthalic acid study report (S0010.7.637.X) was submitted in the NDA CR amendment. Notable issues identified by Dr. Joseph regarding the toxicology studies and the O-phthalic acid study report on 14-June-2007 are that "based on results of the submitted 4-week oral toxicity study of o-phthalic acid in dogs, the 2-year carcinogenicity studies of phthalic anhydride in rats and mice, and other preclinical studies of o-phthalic acid, p-phthalic acid, and phthalic anhydride, the estimated maximum dose of o-phthalic acid resulting from Creon® administration is not considered to be a safety concern."

7.1.12 Special Safety Studies

No special safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No withdrawal or abuse potential is known or suspected with this class of drugs.

7.1.14 Human Reproduction and Pregnancy Data

No studies with Creon MMS were conducted in pregnant women.

It is likely that Creon products will be used by pregnant women and women of reproductive potential. Future labeling should address safety in pregnancy. The Pharmaco-Toxicology review team recommends Pregnancy "Category C"; studies not conducted. This Reviewer concurs with this recommendation.

7.1.15 Assessment of Effect on Growth

The New Infant CF study assessed changes in body mass index (BMI) and weight for height ratio as secondary efficacy parameters. BMI increased from 15.6 (SD 1.7) to 16.3 (SD 1) during the study for a mean increase of 0.7 (SD 1.2; 95% C.I. -1, 1.5). Weight for height ratio showed a mean increase of from 96.8 to 98.8 for mean increase of 2 (SD 6.5; 95% C.I. -2.5, 6.5). The results do not indicate a statistically significant effect on these two growth parameters. Failure to demonstrate an increase in BMI and weight for height in this study occurred because review of the dataset and study report indicates that patients were healthy and not growth deficient at the beginning of the study; therefore, improvement in BMI and weight for height were not expected.

PEPs are widely recognized as having a positive effect on pediatric growth.[1, 2] Studies performed in the Creon clinical development program were, for the most part, short-term studies where long-term growth and development were not assessed, which is consistent with the recommendations for study designs in the Guidance for submitting PEP NDAs. Thus, no formal assessment of pediatric growth and development was expected in the CR amendment.

7.1.16 Overdose Experience

PEPs are not systemically absorbed. An important safety issue regarding PEP use is fibrosing colonopathy (FC). The etiology of FC has not been definitively established, but is thought to be associated with high dose lipase exposure, although some reports indicate the risk of FC is associated with the excipients.[1,5, 6] In order to optimize therapy while minimizing the risk of FC, the Cystic Fibrosis Foundation (CFF), in conjunction with the FDA, recommends starting lipase doses according to age as described below.

The CFF recommends the following dose schedule for full meals:

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.
- Children $\leq$4 years old eating soft or solid foods: begin with 1,000 USP lipase units/kg/meal.
- Children >4 years old: begin with 500 lipase units/kg/meal.
- Doses in excess of 2,500 USP lipase units/kg/meal should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to significantly improve a documented low coefficient of fat absorption.

- The recommended per meal dose should be halved when ingesting snacks.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with fibrosing colonopathy.

The Sponsor's proposed label is unclear. (b) (4) These recommendations should be reflected prominently and accurately in future labeling. Since adoption of the above dosing guidelines, the number of cases of fibrosing colonopathy reported has decreased markedly.

7.1.17 Postmarketing Experience

Creon to-be-marketed-product (TbMP) is not a marketed product, and, therefore, there is no post-marketing experience with the Creon TbMP. The following comments on post-marketing experience refer to Creon currently-marketed-product (CMP) and Creon Microspheres (Creon MS; no longer marketed).

Enteric-coated Creon MS were introduced in Germany in 1982 and Creon MMS debuted in 1993. Creon MS was replaced in the Rest of the World (ROW; includes all countries where Creon is marketed, except the US) by Creon MMS in 2003. The Sponsor states that as of 28-August-2006, marketing authorization for Creon MMS had been granted in 70 non-US countries. As of the date of submission of this NDA update, no Creon MMS product had been withdrawn for safety concerns.

Non-US formulations were marketed as: Creon (Pancrelipase) minimicrospheres, Creon (Pancreatin), Kreon (Pancreatin), Pankreon (Pancreatin), Pankreon forte (Pancreatin), Pankerozym (Pancreatin), Pancrin (Pancreatin), and Papin (Pancreatin). The Sponsor provided a list of 491 post-marketing adverse drug reaction reports associated with different strengths of the different products used by 242 unique foreign and domestic patients. The period of reporting was 01-October-2001 through 20-June-2006.

Deaths and AEs from the post-marketing experience are presented descriptively. Incidence rates of deaths and AEs in the post-marketing experience cannot be determined because the number of exposed patients (the denominator population) is unknown. The Sponsor states 491 post-marketing adverse drug reaction (ADR) reports were received which described events in 242 individuals. No deaths or AEs in the post-marketing experience were reported in the ISS.

Two deaths were reported from the Creon post-marketing experience, as follows:

Report PANC00302001564 is of a 40 year old man with acute gastro-intestinal hemorrhage without stated cause who died from the hemorrhage. The report stated the relationship to Creon products was unlikely.

Report PANC00305002403 is of a 62 year old man who died due to apparent streptococcal-associated necrotizing fasciitis, septic shock, and multiple organ failure while being treated with pancreatin, paracetamol, labetolol hydrochloride, omeprazole, glimepiride, and ibuprofen. Interventions included

multiple antibiotics, ventilation and hemofiltration. The report stated the relationship to Creon products was unlikely.

Gastrointestinal disorders were noted in 41% of post-marketing reports. Other common complaints were skin and subcutaneous tissue disorders (10% of reports), investigations (7% of reports), nervous system disorders (5% or reports), and immune system disorders (2% of reports). The types of AEs reported in post-marketing reports are similar to the types AEs reported in the ISS.

For the MedDRA terms possibly related to fibrosing colonopathy, there was one report each of fibrosing colonopathy, intestinal obstruction, and colitis, which are summarized as follows:

US-SOLVAY-00202000885 reports a 54 year old man with history of pancreatitis who was hospitalized for small intestinal obstruction while taking pancreatin for an unknown period. The patient recovered spontaneously and the relationship to Creon was assessed as possible.

DE-SOLVAY-00305002526 reports a 40 year old woman with nine-day history of recurring diarrhea and tenesmus, and prior medical history of diabetes mellitus, hypertension, hypothyroidism, irritable bowel syndrome, colitis, reflux esophagitis, lactose intolerance, pulmonary embolism, cholecystectomy, appendectomy, hysterectomy, splenectomy, and gastric ulcer. She was being treated with pancreatin. During the hospitalization for the current event, an ileocolonoscopy was performed and showed segmental inflammation in the right colon. She recovered completely and the relationship to Creon products was assessed as unlikely.

US-SOLVAY-00204003851 reports a 25 year old man with cystic fibrosis who had histologically confirmed fibrosing colonopathy. He used multiple PEP products until age 22 years. He was exposed to “Creon 25” for ten months at age 16 years, and continued exposure to other pancreatin products (commercial name not provided) up to age 22 years. The type of PEP and daily lipase unit dose for the intervening period was not reported. The relationship to Creon was assessed as unlikely.

The assessment that the case of FC reported in US-SOLVAY-00204003851 was not related to Creon 25 can not be made from the information provided. Without knowledge of daily lipase dose exposure of any Creon product in the intervening period, the relationship is unknown and ranges from unlikely to probable.

This Reviewer concludes the two post-marketing reported deaths appear related to underlying disease and co-morbidities and do not appear attributable to administration of Creon MMS (CMP). The AEs reported in the post-marketing experience are generally attributable to underlying diseases such as cystic fibrosis and chronic pancreatitis, or unrelated co-morbidities such as cardiovascular disease in the elderly, and do not appear to be causally related to administration of Creon MMS (CMP).

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The description of the Creon primary clinical data sources, clinical development program, patient exposure, and assessments used to evaluate safety are described in detail in the following sections: 1) Section 4 Data Sources, Review Strategy, and Data Integrity; 2) Section 6 Integrated Review of Efficacy; and 3) Section 7 Integrated Review of Safety. Please refer to these sections for additional information.

Safety information was submitted from 57 clinical studies performed between July 1985 and May 2006. Seven studies were not incorporated into the ISS due to data quality issues including inconsistent blinding procedures and lack of study controls, and these studies were not reviewed for safety or efficacy. Sufficient information was provided to allow review of the safety information from the 50 studies in the ISS. The 50 studies in the ISS enrolled a total of 1,546 patients. Of these patients, 743 had cystic fibrosis, 358 had chronic pancreatitis, 153 had pancreatectomy, 109 had diabetes mellitus, 77 had acute pancreatitis, and 109 had other diagnoses. Studies included infants, children, and adults with cystic fibrosis, and adults with chronic pancreatitis and pancreatectomy.

Five trials were analyzed for short-term efficacy and safety. Three trials were performed in patients with cystic fibrosis, including two randomized, double-blind, placebo-controlled trials, and one open-label trial. Two trials were performed in chronic pancreatitis patients, one of which included patients who had undergone pancreatectomy. Both trials were double-blind, placebo-control studies. Original reviews were performed on the New Infant CF and New Adult PEI studies. The Prior Pediatric and Prior Adult CF studies and the Prior Adult CP study were reviewed by Dr. Fathia Gibril during the original review of this NDA (03-December, 2003). Summary comments from Dr. Gibril's review were presented in this review.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary sources of safety information were submitted for review in this CR Amendment.

7.2.3 Adequacy of Overall Clinical Experience

No clinical efficacy and safety studies with Creon to-be marketed product (TbMP) have been performed to date. With the exception of single-dose Creon TbMP exposure in nine patients in the Bridging study, exposure to Creon in the Creon clinical development program has been entirely with Creon CMP or other formulations of Creon that are no longer marketed. Information on exposure to Creon CMP that was submitted to the CR amendment is summarized as follows:

Patients in the ISS may have been exposed to one or more treatments (i.e., Creon MMS, Creon MS, Other PEPs, or placebo). Of 1,546 patients in the ISS, 594 (38%) were exposed to Creon MMS (CMP). Fifty-nine percent (59%) of patients enrolled in CF studies were exposed to Creon MMS;

14% of patients enrolled in CP studies were exposed to Creon MMS; 11% of patients enrolled in post-pancreatic surgery studies were exposed to Creon MMS; and 16% of patients with other primary disorders were exposed to Creon MMS. Eight percent (8%) of patients enrolled in CF studies were exposed to placebo; 54% of patients enrolled in CP studies were exposed to placebo; 13% of patients enrolled in post-pancreatic surgery studies were exposed to placebo; and 26% of patients with other primary disorders were exposed to Creon MMS. These findings are summarized in Table 18 below.

Table 18: Exposure to Treatment Classified by Primary Disease

Studies by Disease Category	Total (N=1546)	Creon MMS (N=594)	Creon MS (N=991)	Other PEP (N=331)	Placebo (N=589)
Cystic Fibrosis, n (%)	743 (48)	351 (59)	574 (58)	277 (90)	49 (8)
Chronic Pancreatitis, n (%)	358 (23)	80 (14)	278 (28)	34 (11)	315 (54)
Post-Pancreatic Surgery[1], n (%)	153 (10)	65 (11)	92 (9)	0 (0)	78 (13)
Diabetes Mellitus, n (%)	109 (7)	55 (9)	0 (0)	0 (0)	54 (9)
Acute Pancreatitis, n (%)	77 (5)	37 (6)	0 (0)	0 (0)	40 (7)
Other[2], n (%)	106 (7)	6 (1)	47 (5)	0 (0)	53 (9)

[1]Pancreatectomy, Gastrectomy [2]HIV, chronic malnutrition

In this Reviewer's opinion, there was adequate exposure of patients with PEI due to CF and other causes (such as CP and post-pancreatic surgery) to Creon MMS and placebo to permit an assessment of the safety of Creon CMP.

For patients included in the ISS, exposure to Creon MMS (CMP) by gender was 64% male and 36% female. The age range of patients exposed to CMP was from one month to 80 years old. Exposure to Creon MMS by race was 70% Caucasian, 11% Asian, 12% where race was categorized as Unknown, 6% where race was categorized as Other (6%), 2% Black, and 0.2% Hispanic. There was a similar Baseline demographic profile for patients exposed to placebo in clinical studies. These findings are summarized in table 19 below (electronically reproduced from Sponsor's table 8.8.8 Volume 26, page 9508).

Table 19: Demographic profile of all patients in ISS

Demographic profile of all patients in ISS	Total	Creon MMS	Creon MS	Other PEP	Placebo
All Patients	1,546	594	991	331	589
Gender					
Male, n (%)	886 (57)	379 (64)	557 (56)	146 (47)	383 (65)
Female, n (%)	619 (40)	215 (36)	393 (40)	124 (40)	206 (35)
Unknown, n (%)	41 (3)	0 (0)	41 (4)	41 (13)	0 (0)
Age (years)					
n (n missing)	1544 (2)	594 (0)	989 (2)	309 (2)	389 (0)
Mean (SD)	34.8 (25.7)	29 (22.7)	29.4 (24)	16.7 (14.9)	52.7 (18.7)
Median	33.6	18.9	16.8	11	52
Min-Max	0.1-103.1	0.1-80	0.4-97.9	2.3-70.1	5.8-103.1
<4 years, n (%)	82 (5)	55 (9)	30 (3)	11 (4)	0^
4-12 years, n (%)	358 (23)	139 (23)	328 (33)	154 (50)	13 (2)
>12-18 years, n (%)	189 (12)	93 (16)	151 (15)	66 (21)	20 (3)
>18-30 years, n (%)	117 (8)	58 (10)	70 (7)	41 (13)	28 (5)
> 30-50 years, n (%)	326 (21)	115 (19)	188 (19)	12 (4)	206 (35)
>50 - ≤ 64 years, n (%)	250 (16)	79 (13)	131 (13)	23 (7)	172 (29)
≥65 years, n (%)	222 (14)	55 (9)	91 (9)	2 (0.6)	150 (25)
Unknown, n (%)	2 (0)	0	2 (0.2)	2 (0.6)	0
Race					
Caucasian, n (%)	1033 (67)	413 (70)	601 (61)	168 (54)	434 (74)
Black, n (%)	32 (2)	10 (2)	17 (2)	0	23 (4)
Asian, n (%)	104 (7)	68 (11)	4 (0.4)	0	99 (17)
Hispanic, n (%)	3 (<1)	1 (<1)	3 (<1)	0	2 (<1)
Other, n (%)	54 (4)	33 (6)	48 (4.8)	0	31 (5)
Unknown, n (%)	320 (21)	69 (12)	318 (32)	143 (46)	0
Weight (kg)					
n (n missing)	1,527 (19)	592 (2)	974 (17)	311	589 (0)
Mean (SD)	49.5 (22.6)	47.3 (23.5)	45.5 (20.6)	36.5 (17.1)	61.7 (17)
Median	49.6	48	45.5	31.2	61
Min-Max	3.3-175	3.3-116.2	10.0-175	10-105	20-175
< 20 kg, n (%)	144 (9)	79 (13)	92 (9)	45 915)	0*
20-40 kg, n (%)	398 (26)	153 (26)	330 (33)	150 (48)	47 (8)
>40-60 kg, n (%)	500 (32)	194 (33)	309 (31)	85 (27)	244 (41)
>60-80 kg, n (%)	341 (22)	111 (19)	199 (20)	26 (8)	217 (37)
>80 kg, n (%)	144 (9)	55 (9)	44 (3)	5 (2)	81 (14)
Unknown, n (%)	19 (1)	2 (0.3)	17 (2)	0	0

^*Does not include 12 patients from S248.3.003 ages 1-24 months, weight less than 20 kg, who underwent open-label non-treatment run-in.

In studies of CF patients, 351 patients were treated with Creon MMS. Of patients treated with Creon MMS, 78% of were treated for less than four weeks, and 18% of patients were treated for between four and eight weeks. In studies of CF patients, 100% of patients treated with placebo (N=49) were treated with placebo for less than two weeks. These findings are summarized in table 20 below.

Table 20: Duration of Exposure in Cystic Fibrosis Studies

Cystic Fibrosis	Total	Creon MMS	Creon MS	Other PEP	Placebo
Exposure (weeks)					
Any, n (%)	743 (100)	351 (100)	574 (100)	277 (100)	49 (100)
<2 weeks, n (%)	27 (4)	44 (13)	83 (15)	65 (24)	49 (100)
2-4 weeks, n (%)	203 (27)	228 (65)	218 (38)	175 (63)	0
>4-8 weeks, n (%)	307 (41)	64 (18)	180 (31)	16 (6)	0
>8-12 weeks, n (%)	112 (15)	12 (3)	12 (2)	10 (4)	0
>12-26 weeks, n (%)	46 (6)	0	40 (7)	11 (4)	0
>26-52 weeks, n (%)	15 (2)	0	11 (2)	0	0
>52 weeks, n (%)	33 (4)	3 (1)	30 (5)	0	0
Exposure (days)					
n	743	351	574	277	49
Mean (SD)	83 (158)	31 (110)	74 (160)	27 (20)	6 (1)
Median	49	16	28	28	6
Min - Max	2 - 1509	3 - 1509	2 - 883	6 - 134	2 - 9
Sum	61,386	10,893	42,686	7,497	310

In studies of CP patients, 80 patients were treated with Creon MMS, all of whom were treated with Creon MMS for less than four weeks, and 315 patients were treated with placebo at some point during the study. Fifty-four percent (54%) of patients treated with placebo were treated with placebo for less than 2 weeks, and 38% of patients were treated with placebo for between two and four weeks. These findings are summarized in table 21 below.

Table 21: Duration of Exposure in Chronic Pancreatitis Studies

Chronic Pancreatitis	Total	Creon MMS	Creon MS	Other PEP	Placebo
Exposure (weeks)					
Any, n (%)	358 (100)	80 (100)	278 (100)	34 (100)	315 (100)
<2 weeks, n (%)	52 (15)	29 (36)	69 (25)	22 (65)	169 (54)
2-4 weeks, n (%)	61 (17)	51 (64)	161 (58)	12 (35)	120 (38)
>4-8 weeks, n (%)	203 (57)	0	48 (17)	0	26 (8)
>8-12 weeks, n (%)	42 (12)	0	0	0	0
>12-26 weeks, n (%)	0	0	0	0	0
>26-52 weeks, n (%)	0	0	0	0	0
>52 weeks, n (%)	0	0	0	0	0
Exposure (days)					
n	358	80	278	34	315
Mean (SD)	36(19)	12 (3)	24 (13)	14 (5)	16 (10)
Median	33	14	28	11	13
Min - Max	4-84	7-17	1-56	9-22	3-47
Sum	12,869	972	6,554	470	4,873

In studies of post-pancreatic surgery patients, 65 patients were treated with Creon MMS, all of whom were treated with Creon MMS for less than four weeks. Seventy-eight (78) patients were treated with placebo, all of whom were treated with placebo for less than four weeks. These findings are summarized in table 22 below.

Table 22: Duration of Exposure in Post-Pancreatic Surgery Studies

Post-Pancreatic Surgery	Total	Creon MMS	Creon MS	Other PEP	Placebo
Exposure (weeks)					
Any, n (%)	153 (100)	65 (100)	92 (100)	0	78 (100.0)
<2 weeks, n (%)	63 (41)	46 (71)	10 (11)	0	66 (85)
2-4 weeks, n (%)	7 (5)	19 (29)	17 (19)	0	9 (13)
>4-8 weeks, n (%)	69 (45)	0	58 (63)	0	3 (4)
>8-12 weeks, n (%)	14 (9)	0	7 (8)	0	0
>12-26 weeks, n (%)	0	0	0	0	0
>26-52 weeks, n (%)	0	0	0	0	0
>52 weeks, n (%)	0	0	0	0	0
Exposure (days)					
n	153	65	92	-	78
Mean (SD)	30.5 (172)	10.2 (3)	34.8 (14)	-	10.2 (7.7)
Median	29	8	38	-	5
Min - Max	2 - 78	8 - 15	6 - 78	-	2 - 29
Sum	4,662	665	3,200	-	797

For all studies reported in the ISS, the Sponsor provided summary data on lipase exposure in lipase units/kg/day. Because multiple studies did not employ both Creon MMS (CMP) and placebo treatment arms, and multiple studies were designed and executed prior to publication of current dosing guidelines,[1] the ability to draw any safety conclusions based on lipase dosing is limited. Therefore, presentation of lipase dosing in this review is provided for descriptive purposes only. For the 351 patients exposed to Creon MMS in CF trials, exposure ranged from 368 to 17,486 lipase units/kg/day. For the 80 patients exposed to Creon MMS in CP trials, exposure ranged from 811 to 3,727 lipase units/kg/day. For the 65 patients exposed to Creon MMS in post-pancreatic surgery trials, exposure ranged from 845 to 8,016 lipase units/kg/day.

This Reviewer concludes that the Sponsor has assessed the short-term safety of Creon CMP in the appropriate disease populations intended for treatment with Creon, including patients with cystic fibrosis and chronic pancreatitis. Appropriate age groups were also studied, including infants, children, adolescents, and adults. The Sponsor's studies of children with cystic fibrosis as young as one month of age are noteworthy, since recently published guidelines recommend screening all US newborns for cystic fibrosis[7], and initiation of PEP therapy in CF is recommended as soon as CF is diagnosed. Infants with CF are, therefore, a likely treatment population for Creon. Thus, in the opinion of this Reviewer, sufficient clinical information has been provided to support a reasonable assurance of the safety of Creon MMS (CMP) in the likely patient treatment populations.

Successful bridging of the Creon CMP and the TbMP was not established; however. Thus, the safety data obtained with Creon CMP cannot be solely relied upon to establish the safety of Creon TbMP, and at least one short-term safety (and efficacy) clinical trials with the TbMP will be required to support an NDA approval for Creon TbMP.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Given the extensive human exposure to PEPs (and to Creon) since before 1938, the Guidance for submitting NDAs states that animal pharmacology studies with the active ingredient (pancrelipase) are not needed to support the Creon clinical development program. However, toxicology studies are needed if the excipients in the Creon drug product are not classified as Generally Recognized as Safe (GRAS). Consistent with the Guidance, only toxicology studies for the excipient O-phthalic acid (under IND 47,546 and study report S0010.7.637.X) were needed. This information has been extensively reviewed by the Toxicology Reviewer (David Joseph, Ph.D; please see section 3.2 Animal Pharmacology/Toxicology of this review). The conclusion of the Toxicology Reviewer is that animal testing was adequate, and based on results of the submitted four-week oral toxicity study of o-phthalic acid in dogs, the two-year carcinogenicity studies of phthalic anhydride in rats and mice, and other preclinical studies of o-phthalic acid, p-phthalic acid, and phthalic anhydride, the estimated maximum dose of o-phthalic acid resulting from Creon administration is not considered to be a safety concern.

7.2.5 Assessment of Quality and Completeness of Data

Safety information from 57 studies was submitted in the CR of this NDA. Seven studies were not incorporated into the ISS due to data quality issues, including missing data elements, and these studies could not be reviewed for safety. Therefore, the ISS only contains information from the remaining 50 studies. Adequate information was provided to allow substantive individual review of two newly submitted studies: the New Infant CF Study and the New Adult PEI Study.

Appropriate patient populations were studied, including patients with cystic fibrosis from one month of age through adulthood, and adult patients with chronic pancreatitis and pancreatectomy. There was adequate representation of both genders. There was a predominance of Caucasian patients in all studies except the New Adult PEI study wherein predominantly Asian patients were enrolled.

In the opinion of this Reviewer, the quality and completeness of the data allowed for substantive review of Creon MMS (CMP) in patients with PEI due to cystic fibrosis and other causes.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The safety results from the Creon clinical development plan are notable for the following.

Deaths

Eight death reports were included in the ISS and ten death reports were received from other sources (post-marketing and global safety surveillance reports). All deaths were attributable to underlying diseases, including recurrence/metastasis of carcinoma and pre-existing cardiovascular or cardiopulmonary disease. No deaths were attributable to Creon MMS (CMP). No pediatric deaths were reported. This Reviewer concludes that the deaths reported in the Complete Response were attributable to underlying disease and were not causally related to use of Creon MMS (CMP).

SAEs and Withdrawals

- In the ISS, SAEs were reported in 3.4% of patients receiving Creon MMS (CMP) and 3.4% of patients receiving placebo. The most common SAEs by System Organ Class (SOC) were gastrointestinal disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders. The most common SAEs by Preferred Term (PT) were pyrexia, cough, acute bronchitis, superinfection of the lung and hypoglycemia. In the opinion of this Reviewer, there was no clinically meaningful difference in incidence or type of SAEs between Creon MMS (CMP) and placebo treatment groups, and the SAEs reported were generally consistent with underlying disease.

- The most common SAEs in children with cystic fibrosis treated with Creon MMS (CMP) in the three pediatric CF safety studies included in the ISS were gastrointestinal disorders, and upper and lower respiratory tract infections. These SAEs appear to be consistent with underlying disease. An increased incidence of SAEs in children treated with Creon MMS (CMP) in these three studies was noted compared to patients treated with placebo (7% compared to 3%). The relevance of this finding is unclear, but may be explained by a greater exposure time of patients to Creon MMS (about 524 patient-weeks of exposure) than to placebo (about 60 patient-weeks of exposure).

- About 3% of patients in the ISS withdrew, including 2% of patients treated with Creon MMS and 3% in patients treated with placebo. The types of AEs leading to withdrawal were similar to the reported SAEs and commonly reported AEs, and appear to be related to underlying diseases and unrelated to administration of Creon MMS (CMP). An increased incidence of withdrawal was noted in patients with acute pancreatitis, which may be explained by the rapidly changing clinical state in patients with acute pancreatitis.

This Reviewer concludes that SAEs and withdrawals reported in the Safety Update were attributable to underlying disease, were expected in the patient populations under study, and did not appear to be causally related to use of Creon MMS (CMP).

Common Adverse Events

AEs were more common in patients treated with Creon MMS (61%) than in patients treated with placebo (49%). This disparity appears to be due to an increased incidence of less commonly reported AEs in the Creon MMS population, such as epistaxis and nasal congestion, than in patients treated with placebo. This disparity may also be due to differences in study designs for studies included in the ISS (e.g., open-label and lack of placebo control in many studies, which limited the placebo experience). However, the types and frequencies of the most commonly reported AEs in the ISS population are substantially similar between patients treated with Creon MMS (CMP) and patients treated with placebo, and include headaches, abdominal pain and other gastrointestinal complaints, respiratory disorders, and upper and lower respiratory tract infections. There were no obvious differences in the types of AEs reported by patients with different Baseline diagnoses or by age.

Special Safety Considerations with PEPs/Creon

Fibrosing colonopathy has been reported in children with Cystic Fibrosis treated with pancreatic enzyme products. No cases of fibrosing colonopathy (FC) were reported in the ISS, which is not unexpected due to the short duration of the studies and the relatively small safety population. One case of FC was reported in post-marketing reports, which was not definitively attributable to treatment with Creon MMS. Monitoring for FC is to be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products.

Hyperuricemia has been reported in patients with pancreatic exocrine insufficiency treated with PEPs. Though blood and urine uric acid monitoring were was not assessed in all studies in the ISS, hyperuricosuria was noted in several patients in the Prior Pediatric CF and Prior Adult CF Studies, all of whom had non-treatment blood uric acid levels near the upper limit of normal. Monitoring for hyperuricemia is to be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products.

In conclusion, in the opinion of this Reviewer, the safety of Creon MMS (CMP) has been adequately assessed. Withdrawals, SAEs, and non-serious AEs reflect findings reported in the original review of this NDA and in open source literature of patients with cystic fibrosis, and other causes of pancreatic exocrine insufficiency, and commonly include headaches, abdominal pain and other gastrointestinal complaints, respiratory disorders, and upper and lower respiratory tract infections. AEs were most commonly attributable to underlying disease and appear unrelated to administration of Creon MMS (CMP). There were no new or notable safety findings with Creon administration reported in the Safety Update of the CR amendment to the NDA. In addition, all of the appropriate patient populations were studied in the Creon CMP clinical development program, including patients with cystic fibrosis as young as one month of age through adulthood, and patients with PEI due to other causes, such as CP.

Since the Bridging study failed to establish the comparability of the Creon CMP and TbMP, the safety results obtained with Creon CMP cannot be solely relied upon to demonstrate the safety of Creon TbMP, and at least one additional short-term safety (and efficacy) study with Creon TbMP will need to be performed to support the NDA approval of Creon TbMP.

7.3.1 Pooling Data across Studies to Estimate and Compare Incidence

The methodology of the three pediatric cystic fibrosis safety studies allowed for pooling of the safety data for these three studies (see section 7.1.2.3 of this review).

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

In order to optimize therapy while minimizing the risk of fibrosing colonopathy (FC), the Cystic Fibrosis Foundation (CFF), in conjunction with the FDA, recommends starting lipase doses according to age as described below.

The CFF recommends the following dose schedule for full meals:

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.
- Children ≤4 years old eating soft or solid foods: begin with 1,000 USP lipase units/kg/meal.
- Children >4 years old: begin with 500 lipase units/kg/meal.
- Doses in excess of 2,500 USP lipase units/kg/meal should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to significantly improve a documented low coefficient of fat absorption.
- The recommended per meal dose should be halved when ingesting snacks.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with fibrosing colonopathy.

Because safety and efficacy of the Creon TbMP have not been demonstrated in clinical trials, the final dose recommendations may change based on results of clinical trials of the TbMP; however, dosing recommendations for the TbMP should be consistent with current Cystic Fibrosis Foundation guidelines. The Sponsor's proposed dosing in the draft labeling for the CMP for pediatric patients be weight-based, and was generally consistent with the CFF guidelines.

For adult patients with CP and pancreatectomy (PY), dosing should be individualized. The Sponsor recommends an adult starting dose of (b) (4) This Reviewer notes the upper limit of these doses exceeds the highest dose administered in clinical trials of CP and PY patients. This Reviewer recommends that the maximum doses in final labeling not exceed the maximum doses studied for these indications.

8.2 Drug-Drug Interactions

It is expected that patients with PEI may be exposed to prokinetic agents, H-blocking anti-histamines, and antacids. The efficacy studies included in the CR amendment allowed patients to be on these medicines if the dose was stable at the beginning and throughout study. In addition, many patients included in the studies in the CR amendment were on a large number and variety of medications for

treatments of co-morbidities associated with underlying disease (e.g., antibiotics for infectious complications of CF). No reports of drug-drug interactions were noted in the CR amendment. Since Creon is not systemically absorbed, no interactions with systemically-active medications would be expected, although drug-drug interactions were not formally assessed as part of the Creon clinical development program.

8.3 Special Populations

The Creon clinical development program was conducted in patients where PEI is part of primary pathophysiology, including CF, CP, and PY, and in processes where PEI may present less commonly (e.g., diabetes mellitus). The clinical development program focused mainly on patients with CF, CP and PY.

Cystic fibrosis is an autosomal recessive disease estimated to occur in about 1 in 1,500 to 1 in 2,500 live births in the US, and affects an estimated 30,000 persons in the US. No cure exists but supportive treatment with anti-infectives, pancreatic enzyme supplements, and pulmonary, cardiac, and hepatic support has extended life expectancy out of childhood into the fourth and fifth decades. A majority of patients with CF have PEI, and CF patients account for about 42% of the population in the five key studies reviewed (New Infant CF, New Adult PEI, Prior Pediatric CF, Prior Adult CF, and Prior Adult CP Studies). The capacity to respond to treatment, demonstrated by increase in %CFA, appears to mirror severity of PEI, with more severely affected patients demonstrating greater response. This trend in response was seen in infants, youths, and adults with CF.

Studies in patients with cystic fibrosis included patients of both genders. The Sponsor provided information on children from one month of age through adulthood. The Sponsor provided safety information on children with cystic fibrosis less than seven years of age, and provided efficacy data on infants from one through 23 months of age. Adults with cystic fibrosis, from 18 to 53 years were also studied. Though the number of patients studied was small, males and females with CF appear to respond similarly. As expected, from epidemiological characteristics of cystic fibrosis, the CF population studied was predominantly Caucasian; therefore, there is insufficient information to determine any difference in response to treatment in CF patients based on ethnicity.

Pancreatectomy produces definitive and severe PEI. Pancreatectomy is a rare circumstance, offered as a component of treatment for certain gastric or pancreatic cancers, or as a result of trauma care. Patients with PY account for about 29% of the population in the five key studies. Similar to patients with CF, patients with more severe baseline disease demonstrated greater response.

In the opinion of this Reviewer, patients likely to be treated with Creon in the post-marketing setting, including the special populations noted above, have been adequately studied with Creon CMP in the Creon clinical development program.

8.4 Pediatrics

Cystic fibrosis is traditionally diagnosed in childhood, and with the adoption of new screening methods, diagnosis is expected to take place in infancy (e.g., within several weeks of birth). Many children with cystic fibrosis typically display signs and symptoms of malnutrition and pancreatic enzyme deficiency within several months of birth. Because pancreatic enzyme replacements are a mainstay of treatment of patients with pancreatic exocrine insufficiency, it is likely that Creon MMS would be used in infants with CF.

Efficacy was demonstrated in two studies of children from infancy through 17 years of age. In one study of 12 infants from one through 23 months of age, an increase in stool CFA from non-treatment baseline was demonstrated. A second study of 36 children with CF ages 7 through 17 years, also demonstrated benefit (by mean CFA) for the treatment of these patients with Creon. This Reviewer concludes that these efficacy results support the use of Creon MMS (CMP) in children, from one month through 17 years of age.

Two hundred eighty seven (287) children with cystic fibrosis between the ages of one month and 18 years were included in safety analyses. There were 55 children from one month through three years old, 139 children from four through 11 years, and 93 children from 12 through 17 years. It is this Reviewer's opinion that a sufficient number children with cystic fibrosis treated with Creon MMS (CMP) were included to allow analysis of safety in children, including infants as young as one month of age.

This Reviewer concludes that sufficient information was submitted to support the safety and efficacy of Creon MMS (CMP) in children, and children do not appear to respond differently to treatment with Creon than do adults. However, because the Bridging study failed to link the TbMP and CMP, safety and efficacy of the TbMP has not been demonstrated in children.

8.5 Advisory Committee Meeting

No Advisory Committee was convened for this application.

8.6 Literature Review

PEI is well described in the literature as is the use CFA as a measure of efficacy in patients with PEI due to CF [1, 2, 3]. A systematic literature review was not performed.

A list of bibliographic references incorporated into the text of this review is located in Appendix 10.3 of this review.

8.7 Postmarketing Risk Management Plan

No post marketing risk management plan is recommended at this time.

8.8 Other Relevant Materials

There are no other relevant materials being considered.

9 OVERALL ASSESSMENT

9.1 Conclusions

The short-term clinical efficacy and safety of the Creon currently marketed product (CMP) have been demonstrated in children (ages one month through 18 years) and adults with cystic fibrosis (CF), and in adults with pancreatic exocrine insufficiency due to chronic pancreatitis and pancreatectomy. However, a comparison of the Creon CMP and the to-be-marketed product (TbMP) in the Bridging study failed to establish the comparability of the Creon CMP and the TbMP. Therefore, data in this CR amendment are not adequate to support the approval of Creon TbMP. At least one new, short-term clinical efficacy and safety trial with the Creon TbMP will be required for approval of the Creon TbMP, and should be conducted in accordance with the recommendations outlined in the Guidance for submitting PEP NDAs.

9.1.1 Efficacy

Two new short-term clinical efficacy and safety trials of Creon MMS (CMP) in patients with PEI were submitted in this CR amendment to the NDA and were reviewed for efficacy. Three short-term clinical efficacy and safety trials of Creon MMS (CMP) were submitted in the original NDA, and have been previously reviewed and summarized for efficacy during the original NDA review cycle. These five studies collectively enrolled 86 patients with CF, ranging in age from one month to 53 years, and 121 adult patients with PEI due to chronic pancreatitis (CP; n=62), and pancreatectomy (PY, n=59). The primary efficacy measure in these studies was coefficient of stool fat absorption (CFA) from non-treatment or placebo treatment compared with CFA during treatment with Creon MMS (CMP).

Efficacy results from studies are summarized below.

- New Infant CF Study (S248.3.003): In this short term, open-label study of 12 infants with CF, between one and 24 months of age, mean increase in CFA with Creon treatment compared to a no-treatment Baseline was 27% (95% C.I. 12.3, 41.1). Increase in CFA was greatest in four patients with non-treatment CFA less than 40%. Statistical inferences could not be made due to the small size of the study; however the clinical findings showed a clinically meaningful benefit of Creon treatment, and the magnitude of the results are similar to results seen in older pediatric and adult patients with CF. Thus, this study supports the clinical effectiveness of Creon CMP treatment of infants with PEI due to CF as young as one month of age.

- New Adult PEI Study (S245.3.115): In this short term, double-blind, placebo-controlled trial of low-dose and high-dose Creon MMS (CMP) in patients with PEI due to CP (N=35) and PY (N=59), mean increase in CFA for the ITT population (CP and PY) was 12% in patients

receiving high-dose Creon MMS (CMP) compared to placebo (p-value 0.015). In the pancreatectomy sub-population, increase in CFA was approximately 18% in the high-dose Creon group compared to placebo (p-value 0.011). No significant difference in mean CFA compared to placebo was demonstrated in the low-dose Creon group (overall or by sub-population), or in CP patients treated with either low-dose or high-dose Creon CMP.

The Sponsor performed an unplanned interim analysis during the study, and the potential effects on measure of statistical success were not provided. Therefore, no statistical inferences can be made for this study, and this Reviewer concludes that the results of the Adult PEI Study can not be used to support the efficacy of Creon CMP treatment for PEI due to CP or PY.

- Prior Pediatric CF Study (S223.3.101): In this short term, randomized, double-blind, placebo-controlled, treatment withdrawal trial of 38 children with CF, aged 7 through 17 years, CFA was 31% higher (p-value < 0.001) in the Creon MMS (CMP) treatment group (N=18) compared to the placebo group (N=20). These findings show a statistically significant and clinically meaningful benefit of Creon treatment in pediatric patients with PEI due to CF, ages seven years and older.

- Prior Adult CF Study (S223.2.102): In this short term, randomized, double-blind, placebo-controlled, treatment withdrawal trial of 36 adults with CF, ages 18 through 53 years, CFA was 35% higher (p-value < 0.001) in the Creon MMS (CMP) treatment group (N=18) compared to the placebo group (N=18). These findings show a statistically significant and clinically meaningful benefit of Creon treatment in adult patients with PEI due to CF, ages eighteen and older.

- Prior Adult PEI Study (S223.2.01): In this short term, randomized, double-blind, placebo-controlled, treatment trial of 27 adults with CP, ages 38 through 74 years, CFA was 16% higher (p-value 0.0185) in the Creon MMS (CMP) treatment group (N=12) than the placebo group (N=14). These findings show a clinically meaningful benefit of Creon treatment in adult patients with PEI due to CP.

In conclusion, it is the overall assessment of this Reviewer that data from three short-term clinical efficacy and safety studies conducted in pediatric and adult patients with CF, and adult patients with CP support the effectiveness of Creon CMP treatment of steatorrhea in patients with EPI, and that Creon's effectiveness appears to be greatest in the most severely affected patients (i.e., patients with the lowest Baseline CFA). Results from the New Infant CF study were supportive of the clinical effectiveness of Creon CMP in the treatment of steatorrhea in infants with CF, ages one to 24 months these patients, and the results from this study were consistent with the results seen in clinical studies in older pediatric and adult patients. These findings support the labeling of Creon CMP for the treatment of steatorrhea in patients with EPI, ages one month to adult. The results from the New Adult PEI study cannot be used to support the effectiveness of Creon CMP in the treatment of EPI, due to problems with study conduct, and because of the results of the study were not clinically meaningful.

The Sponsor intends to market the Creon TbMP. However, no efficacy and safety clinical trials have been conducted to date with the Creon TbMP. The Bridging study that was submitted to the CR

amendment, and was conducted for the purpose of demonstrating the comparability of the Creon CMP and TbMP products, failed to demonstrate the clinical comparability of the two products. Thus, the efficacy and safety results from studies with the Creon CMP cannot be used to support the clinical efficacy and safety of the Creon TbMP. Therefore, the efficacy (and safety) of the Creon TbMP for the treatment of steatorrhea in patients with EPI has not been demonstrated, and the information submitted in this CR amendment does not support the approval of Creon TbMP.

9.1.2 Safety

The Safety Update in this CR amendment contains information from 57 clinical studies conducted between July 1985 and May 2006, and performed with Creon MMS (CMP) or other formulations that are no longer marketed (e.g., Creon MS). Of the 57 studies in the ISS, 52 are multiple-dose studies and five are single-dose studies. Safety information from 12 of the 57 studies is submitted for the first time in this CR amendment. Seven studies were not incorporated into the ISS due to data quality issues (e.g., inadequate methods for data collection, and incomplete safety datasets), and were not included in this safety review. Therefore, the ISS contains safety information from 50 studies.

The safety results are notable for the following:

Deaths

Eight death reports were included in the ISS and ten death reports were received from other sources (post-marketing and global safety surveillance reports). All deaths were attributable to underlying diseases, including recurrence/metastasis of carcinoma and pre-existing cardiovascular or cardiopulmonary disease. No deaths were attributable to Creon MMS (CMP). No pediatric deaths were reported. This Reviewer concludes that the deaths reported in the Complete Response were attributable to underlying disease and were not causally related to use of Creon MMS (CMP).

SAEs and Withdrawals

- In the ISS, SAEs were reported in 3.4% of patients receiving Creon MMS (CMP) and 3.4% of patients receiving placebo. The most common SAEs by System Organ Class (SOC) were gastrointestinal disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders. The most common SAEs by Preferred Term (PT) were pyrexia, cough, acute bronchitis, superinfection of the lung and hypoglycemia. In the opinion of this Reviewer, there was no clinically meaningful difference in incidence or type of SAEs between Creon MMS (CMP) and placebo treatment groups, and the SAEs reported were generally consistent with underlying disease.

- The most common SAEs in children with cystic fibrosis treated with Creon MMS (CMP) in the three pediatric CF safety studies included in the ISS were gastrointestinal disorders, and upper and lower respiratory tract infections. These SAEs appear to be consistent with underlying disease. An increased incidence of SAEs in children treated with Creon MMS (CMP) in these three studies was noted compared to patients treated with placebo (7% compared to 3%). The relevance of this finding is unclear, but may be explained by a greater exposure time of patients

to Creon MMS (about 524 patient-weeks of exposure) than to placebo (about 60 patient-weeks of exposure).

- About 3% of patients in the ISS withdrew, including 2% of patients treated with Creon MMS and 3% in patients treated with placebo. The types of AEs leading to withdrawal were similar to the reported SAEs and commonly reported AEs, and appear to be related to underlying diseases and unrelated to administration of Creon MMS (CMP). An increased incidence of withdrawal was noted in patients with acute pancreatitis, which may be explained by the rapidly changing clinical state in patients with acute pancreatitis.

This Reviewer concludes that SAEs and withdrawals reported in the Safety Update were attributable to underlying disease, were expected in the patient populations under study, and did not appear to be causally related to use of Creon MMS (CMP).

Common Adverse Events

AEs were more common in patients treated with Creon MMS (61%) than in patients treated with placebo (49%). This disparity appears to be due to an increased incidence of less commonly reported AEs in the Creon MMS population, such as epistaxis and nasal congestion, than in patients treated with placebo. This disparity may also be due to differences in study designs for studies included in the ISS (e.g., open-label and lack of placebo control in many studies, which limited the placebo experience). However, the types and frequencies of the most commonly reported AEs in the ISS population are substantially similar between patients treated with Creon MMS (CMP) and patients treated with placebo, and include headaches, abdominal pain and other gastrointestinal complaints, respiratory disorders, and upper and lower respiratory tract infections. There were no obvious differences in the types of AEs reported by patients with different Baseline diagnoses or by age.

Special Safety Considerations with PEPs/Creon

Fibrosing colonopathy has been reported in children with Cystic Fibrosis treated with pancreatic enzyme products. No cases of fibrosing colonopathy (FC) were reported in the ISS, which is not unexpected due to the short duration of the studies and the relatively small safety population. One case of FC was reported in post-marketing reports, which was not definitively attributable to treatment with Creon MMS. Monitoring for FC is to be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products.

Hyperuricemia has been reported in patients with pancreatic exocrine insufficiency treated with PEPs. Though blood and urine uric acid monitoring were was not assessed in all studies in the ISS, hyperuricosuria was noted in several patients in the Prior Pediatric CF and Prior Adult CF Studies, all of whom had non-treatment blood uric acid levels near the upper limit of normal. Monitoring for hyperuricemia is to be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products.

In conclusion, in the opinion of this Reviewer, the safety of Creon MMS (CMP) has been adequately assessed. Withdrawals, SAEs, and non-serious AEs reflect findings reported in the original review of this NDA and in open source literature of patients with cystic fibrosis, and other causes of pancreatic exocrine insufficiency, and commonly include headaches, abdominal pain and other gastrointestinal complaints, respiratory disorders, and upper and lower respiratory tract infections. AEs were most commonly attributable to underlying disease and appear unrelated to administration of Creon MMS (CMP). There were no new or notable safety findings with Creon administration reported in the Safety Update of the CR amendment to the NDA. In addition, all of the appropriate patient populations were studied in the Creon CMP clinical development program, including patients with cystic fibrosis as young as one month of age through adulthood, and patients with PEI due to other causes, such as CP.

Since the Bridging study failed to establish the comparability of the Creon CMP and TbMP, the safety results obtained with Creon CMP cannot be solely relied upon to demonstrate the safety of Creon TbMP, and at least one additional short-term safety (and efficacy) study with Creon TbMP will need to be performed to support the NDA approval of Creon TbMP.

9.1.3 Conclusion

In conclusion, it is the overall assessment of this Reviewer that data from three clinical short-term efficacy and safety studies conducted in pediatric and adult patients with CF, and in adult patients with CP support the effectiveness of Creon CMP treatment of steatorrhea in patients with PEI. Creon's effectiveness appears to be greatest in the most severely affected patients (i.e., patients with the lowest Baseline CFA). Results from the New Infant CF study were also supportive of the clinical effectiveness of Creon CMP in the treatment of steatorrhea in infants with CF, ages one to 24 months these patients, and the results from this study were consistent with the results seen in clinical studies in older pediatric and adult patients. These findings support the labeling of Creon CMP for the treatment of steatorrhea in patients with PEI, ages one month to adult. The results from the New Adult PEI study can not be used to support the effectiveness of Creon CMP in the treatment of EPI, due to problems with study conduct, and because of the results of the study were not clinically meaningful.

The safety of Creon CMP has also been supported in the short-term clinical efficacy and safety studies, and by the information in the ISS/Safety Update submitted for review in the CR amendment. Overall, no new or notable safety signals were identified in the review of the safety data, the adverse event profile of Creon CMP is felt to be consistent with the profile of Creon (and other PEPs) previously described, and the majority of AEs reported appear to be consistent with underlying disease.

The Sponsor intends to market the TbMP. However, no efficacy and safety clinical trials have been conducted to date with the Creon TbMP. The Bridging study that was submitted to the CR amendment, and was conducted for the purpose of demonstrating the comparability of the Creon CMP and TbMP products, failed to demonstrate the clinical comparability of the two products. Thus, the efficacy and safety results from studies with the Creon CMP cannot be used to support the clinical efficacy and safety of the Creon TbMP. Therefore, the efficacy and safety of the Creon TbMP for the

treatment of steatorrhea in patients with EPI has not been demonstrated, and the information submitted in this CR amendment do not support the approval of Creon TbMP.

9.2 Recommendation on Regulatory Action

This Reviewer recommends an Approvable (AE) action.

The safety and efficacy of the Creon MMS (CMP) have been established for the treatment of steatorrhea in patients with PEI, ages one month to adult. However, except for one bridging study, no clinical trials have been performed with the Creon to-be-marketed product (TbMP). The bridging study failed to establish the clinical comparability of the CMP and TbMP. Therefore, data in this CR are not adequate to support the approval of Creon TbMP.

One or more short term, efficacy and safety clinical trials with Creon TbMP are required to establish the safety and efficacy of the Creon TbMP. These studies are to be performed in patients with pancreatic exocrine insufficiency, such as cystic fibrosis. Efficacy in these clinical trials is to be demonstrated by a change in coefficient of stool fat absorption (CFA) from non-treatment or placebo treatment compared to CFA during treatment with the TbMP.

9.3 Recommendation on Postmarketing Actions

No post-marketing actions are recommended at this time.

9.4 Labeling Review

This Reviewer recommends an approvable action; therefore, review of labeling was not performed.

9.5 Comments to Applicant

Study S245.2003 (e.g., the Bridging study) failed to bridge the currently marketed product (CMP) to the to-be marketed product (TbMP). Therefore, safety and efficacy information of the CMP can not be used to establish safety and efficacy of the TbMP.

One or more a short term, clinical trials of efficacy and safety of Creon MMS (TbMP) are required to establish safety and efficacy of the TbMP. These studies are to be performed in patients with pancreatic exocrine insufficiency, such as cystic fibrosis. Efficacy in these clinical trials is to be demonstrated by a change in coefficient of stool fat absorption (CFA) from non-treatment or placebo treatment compared to CFA during treatment with the TbMP.

Interim analyses may weaken or invalidate statistical inferences of efficacy and should be avoided. If performed, details of planned interim analyses are to be included in your initial study protocol.

Future clinical trials of the TbMP are to be in accordance with the FDA Draft Guidance Document: Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs (located here http://www.fda.gov/Cder/guidance/6275fnl.htm).

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 New Infant CF Study (S248.3.003)

The study was performed with a CMP formulation of MMS, rather than with the TbMP.

10.1.1.1 Study Design

This was an eight-week, open-label, single arm, two-center study of 12 infants, one to 24 months old, that evaluated the efficacy, safety and tolerability of Creon for Children (a brand of Creon MMS) in patients with pancreatic PEI due to CF. On day -10, after screening and informed consent procedures were completed, enrolled patients discontinued prior PEP therapy, if any, at least 72 hours prior to initial dietary fat monitoring and stool collection for Baseline CFA evaluation [day -7 to day -4]. Treatment began on day 1 with a Creon MMS dose of 2,000 lipase units per gram of fat intake. Maximum daily dose was not stated in the protocol. Stool collection for the second CFA (Treatment CFA) was repeated at visit 2 (treatment day 15). Both Baseline and Treatment CFA were both performed during hospitalization for 72-hour fat balance assessment. Safety and secondary efficacy parameters were assessed at visits three (day 36) and four (day 57).

Eligible patients were one to 24 months old with CF, and PEI defined either by age adjusted definitions of steatorrhea or stool chymotrypsin < 5 U/g stool. Patients were required to have Baseline CFA < 70%.

The primary efficacy endpoint was change in CFA (Treatment CFA minus Baseline CFA). Success was defined as Treatment period CFA > 90%. Secondary efficacy measures were effect on steatorrhea and growth parameters including height, weight, and body mass index.

No placebo treatment was administered during Baseline (e.g., wash-out) or Treatment periods. Regardless of prior exposure to any PEP, all patients underwent at least a 72-hour wash-out period prior to the first 72-hour dietary intake assessment and fat balance assessment and subsequent treatment. Patients served as their own controls.

The first patient's first visit was on 27 June 2002, and the final patient's last visit was on 7 September 2004.

10.1.1.2 Study Objectives

Primary objectives were efficacy and safety. The main efficacy parameter was change in CFA Treatment CFA minus Baseline CFA). Successful response was defined as patients with treatment CFA above 90%.

Secondary objectives were evaluation steatorrhea, fecal energy balance, stool characteristics, gastrointestinal symptoms, laboratory parameters; nutritional parameters including weight, height, and weight for height percentile; and patient acceptance.

Note that efficacy will be determined only change in CFA. It is expected that treatment with PEPs positively affects growth parameters in children with CF; however, the study was not of sufficient duration for potential changes in these parameters to be adequately assessed.

10.1.1.3 Eligibility Criteria

Patients were to be between one to 24 months old with a diagnosis CF diagnosed by either two sweat tests or gene analysis, must have had PEI defined by age adjusted steatorrhea (< 4 months, > 4 g/24 hr; 4-12 months, > 3 g/24 hr; > 12 months, > 3-4 g/24 hr) or stool chymotrypsin < 5 U/g stool, and must have had baseline CFA < 70% at end of non-treatment wash-out period.

Patients were excluded if they had severe illness, or other relevant diseases revealed by history, physical, or laboratory assessments which might limit participation in the study. Specific exclusions included clinically evident chest disease, abnormal chest x-ray, meconium ileus or other conditions requiring intestinal resection, allergy to porcine pancreatin, sever allergy or sever abnormal drug reaction, any pancreatic enzyme therapy within three days prior to first hospitalization (Baseline CFA), and any experimental drug within 4 weeks prior to study entry.

10.1.1.4 Concomitant and Prohibited Medications

Any pre-study PEP had to be discontinued at least 72 hours prior to day 1. The following classes of medicines were prohibited except if already in use at a fixed dose at screening: prokinetic agents, antacids, H2 antagonists, proton-pump inhibitors, sucralfate, prostaglandins, CCK-antagonists, biliary acids, and taurine. Any other medicines that were medically required during the study were reported on CRFs.

10.1.1.5 Study Visits and Procedures

Study visits and Procedures are presented in Table 23 below.

Table 23: New Infant CF Study: Flow Chart of Study Visits and					
Phase	**Screening**	**Baseline**	**Treatment**		
	Day -10	Day 1 Visit 1	Day 15 Visit 2	Day 36 Visit 3	Day 57 Visit 4
Hospitalization	Day (-7 to -4)		(Day 12 to 15)		
Demographics	X				
Physical Exam	X				X
Informed Consent	X				
Vital Signs	X	X	X	X	X
Inclusion/Exclusion	X	X			
Chymotrypsin	X		X		
Stool studies[1]	X				
Weight, height, weight for height percentile	X	X	X	X	X
Baseline Complaints		X			
Concomitant Medications		X	X	X	
Lab Assessments[2]	X				
Gastrointestinal symptoms		X	X	X	X
Patient's acceptance			X	X	X
AE collection			X	X	x
Dispense Drug		X	X	X	
Drug collection/compliance review			X	X	X
Diary review		X	X	X	X

[1] CFA, steatorrhea, stool weight, stool consistency, fecal energy loss
[2] Hemoglobin, hematocrit, RBC and WBC count, cholesterol, total protein, serum albumin, blood iron, vitamins A and E

10.1.1.6 Randomization, Blinding and Controls

There was no randomization or blinding. This was an open-label, uncontrolled study.

10.1.1.7 Study Medication Dose Selection, Dispensing, and Compliance

All patients received the same drug dose based on grams of fat intake per-meal.

Creon for Children (batch number 15601) was supplied in glass bottles containing a maximum of 20 g Creon for Children MMS (CMP). The MMS were 0.7 to 1.0 mm. The bottles were packaged with a metered dose spoon. The Sponsor states one dose measure (100 mg MMS) contained 60.36 mg pancreatin with the following enzyme values:

Lipase 5,000 Ph Eur Units
Amylase 3.600 Ph Eur Units
Protease 200 Ph Eur Units

10.1.1.8 Efficacy and Endpoint Measures

The primary outcome measures were stool CFA and safety. Primary efficacy was defined as Treatment CFA minus Baseline CFA. Safety outcomes included any clinically meaningful changes from screening or Baseline, and AE occuring from the beginning of treatment with Creon MMS.

10.1.1.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint was Treatment CFA minus Baseline CFA. Statistical significance was analyzed using a paired t-test. Efficacy was assessed for the ITT and PP population.

10.1.1.8.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints were change in mean stool fat, change in mean stool weight, and increase in dietary fat.

10.1.1.8.3 Safety Assessments

Safety was assessed by type and incidence of AEs; discontinuations due to AEs; drug related AEs, SAEs, and severe AEs; changes from screening visit or Baseline visit in physical exam. vital signs, or clinical laboratory assessments.

10.1.1.8.4 PK and PD Measures

PEPs act locally in the gastrointestinal tract and are not systemically absorbed. Therefore, PK and PD measures were not performed as part of this study.

10.1.1.9 Additional Statistical Considerations

Changes in % CFA are presented as continuous variables, and were summarized by minimum, median, and maximum reported % CFA value, arithmetic mean, standard deviation, and the number of CFA observations. Secondary outcomes (e.g., number of stools per day) were categorical variables and results were summarized absolute and relative frequencies.

10.1.1.10 Protocol Amendment

Due to slow accrual of patients, a single protocol amendment increased the number of study centers from one to two.

10.1.1.11 Study Conduct

The sponsor states the study was performed under ICH/GCP Guidelines. No financial interests were reported.

10.1.1.12 Study Results

10.1.1.12.1 Patient Population and Demographics

Twelve patients were screened, enrolled, and completed the study. The population was comprised of five male and seven female children between the ages of one and 23 months. All patients were Caucasian.

The first dose was administered 06-July-2002, and the final dose was administered 04-September-2004.

10.1.1.12.2 Concomitant Medication

Patients were exposed to 29 non-study medications, including two non- protocol PEPs, administration of which ceased six or greater days prior to the protocol drug treatment dose.

The most common concomitant medications were tocopherol acetate (N=9), multivitamin preparations (N=9), and antibiotics (N=9; Augmentin=1, Ciprofloxacin=2, Colistin=1, Tobral=1, Zimox=1, and Zithromax=3) for treatment of mild to moderate inter-current infections and prophylaxis. Table 27 below lists all concurrent medications. Table 24 below lists concomitant study medications during Creon MMS (CMP) treatment.

Table 24: New Infant CF Study: Most Common Concomitant Medications

Concomitant Medications During Treatment	N (%)
Any concomitant Medication	12 (100)
Other, Plain Vitamin Preparations	12 (100)
Protovit (multivitamin)	9 (75)
Macrolides (Azithromycin)	4 (33)
Paracetamol	3 (25)
Phytomenadione	3 (25)
Prednisone (systemic)	3 (25)

10.1.1.12.3 Compliance with Study Medication

The sponsor states that "poor documentation of compliance" precluded analysis. A record of dispensed and returned medication and weight of unused drug is reported.

Mean exposure time was 59 days (57-64 days).

Mean lipase dose in lipase units/gram/day of fat intake was 2,326 (SD 1,274). Median dose was 1,910 lipase units/gram fat intake/day, and dose range was from 1,159 to 5,148 lipase units/gram fat intake/day.

Mean daily lipase dose was 7,967 u/kg/day (SD 2,071). Table 25 below displays each patients average estimate of average daily dose based on each patient's mean weight over the study period and each patients mean daily dose. Each line represents one patient. All patients are presented.

Table 25: New Infant CF Study Estimated Mean Daily Dose, ITT

	Average Measured Daily Doses	Activity Lipase Units/day	Average Daily Weight (kg)	Mean Daily Dose IU/kg/day
	15.4	77,000	10.6	7,264
	7.5	37,500	5	7,500
	15.5	77,500	11.3	6,858
	25.5	127,500	12.4	10,282
	5.6	28,000	4.1	6,829
	10.3	51,500	6.6	7,803
	11.9	59,500	7.7	7,727
	12.7	63,500	8.5	7,471
	8.4	42,000	8.7	4,827
	30.6	15,3000	11.7	13,077
	9.4	47,000	6.8	6,912
	12.5	62,500	6.9	9,058
Mean	**13.7**	**68,875**	**8.4**	**7,967**
SD	**7.4**	**36,890**	**2.7**	**2,071**

10.1.1.12.4 Protocol Deviations and Violations

Datasets were reviewed and compared with listed protocol deviations and violations. Two patients had major protocol violations (Baseline CFA over 70%). All patients had minor protocol deviations. All patients completed all treatment procedures. All protocol deviations are listed in Table 26 below, copied from Submission vol. 60 p 21,945

Table 26: New Infant CF Study: Protocol Deviations

Category of Deviation	N=12	% Affected
Number of Patients with at Least One Deviation	10	(83.3%)
ASSESSMENT SCHEDULE	8	(66.7%)
Diary entries completely missing on one or more of the planned days	4	(33.3%)
Diary entries incomplete but not completely missing on one or more days	3	(25.0%)
Visit 4 not 56 days +/- 5 days after Visit 1	2	(16.7%)
Duration of stool collection other than 3 days	1	(8.3%)
First screening visit more than 10 days before Visit 1	1	(8.3%)
Last day of second hospitalization not one day before Visit 2	1	(8.3%)
Visit 3 not 35 days +/- 3 days after Visit 1	1	(8.3%)
IN-/EXCLUSION CRITERIA	4	(33.3%)
Deviation from inclusion or exclusion criterion as ticked on CRF pages	4	(33.3%)
Age < 1 or > 24 months	2	(16.7%)
Patient's baseline CFA is ≥ 70%	2	(16.7%)

Patients 1-6 and 2-3 had Baseline CFAs of 71.4 and 70.3%, respectively, which qualified as major protocol violations. Both patients were female. No other protocol deviations resulted in alterations in the ITT or PP populations. The sponsor's table below lists all protocol deviations.

This reviewer determined the two patients with Baseline CFA over 70% should be retained in primary efficacy analysis calculations because their Baseline CFA results were virtually identical to the 70% cut-off given published performance characteristics of the method of CFA analysis.[8]

This reviewer concludes the protocol deviations do not preclude analysis and interpretation of any patient's results.

10.1.1.12.5 Efficacy Analyses

10.1.1.12.5.1 Primary Efficacy Analyses

Primary efficacy is defined as change in CFA (Treatment CFA minus Baseline CFA) in the ITT population. Stool for Baseline CFA was collected starting at ≥ 72 hour non-treatment/wash-out. Stool collection for Treatment CFA began at the two week treatment visit (15th day or Creon MMS treatment).

Mean Baseline CFA for the ITT was 58% (SD=18), mean Treatment CFA was 85% (SD=12), and change in mean CFA was 27% (SD=22, 95% C.I. = 12.9, 40.4). The results are clinically meaningful; however, the Statistician's review indicates the study was not of adequate size to draw statistical inferences. Percentages are rounded to nearest whole number integer.

This reviewer performed an unplanned subgroup analysis which evaluated change in CFA based on Baseline CFA (< 60% and ≥ 60%). In the population with Baseline CFA < 60%, mean Baseline CFA was 41% (SD=25), and mean change in CFA was 43% (SD=27, 95% C.I. = -0.9, 86.1). Individuals with Baseline CFA ≥ 60% had mean Baseline CFA of 66% (SD 4) and mean change in CFA was 19% (SD=14, 95% C.I. = 6.8, 30.6). These results are clinically meaningful but due to the sizes of the study sub-populations no statistical inferences can be made. Percentages in text are rounded to nearest whole number integer. These findings are presented in Tables 27 and 28, and Figure 5 below.

Table 27: New Infant CF Study; Change in CFA (%) by Baseline CFA (%) Category for ITT Population

	All Patients	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: Statistical Reviewer's analysis

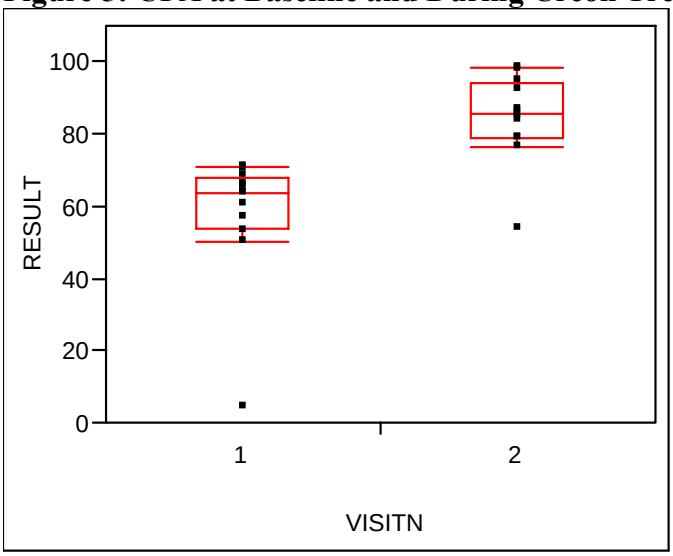
Table 28: New Infant CF Study: Individual Patient Change in CFA Treatment CFA minus Baseline CFA (Mean, SD); ITT

ITT population (N=12)			
	Baseline CFA	Treatment CFA	Change in CFA
	4.7	85.1	80.4
	50.3	95.0	44.7
	53.3	76.5	23.2
	57.1	79.0	21.9
	60.5	98.6	38.1
	63.7	54.3	-9.4
	63.8	87.1	23.3
	65.8	84.1	18.3
	66.5	86.7	20.2
	68.9	98.3	29.4
	70.3	79.1	8.8
	71.4	92.5	21.1
Mean	**58.0**	**84.7**	**26.7**
SD	**18**	**12.1**	**21.7**
CFA (Mean, SD); Baseline CFA < 60% (N=4)			
	4.7	85.1	80.4
	50.3	95	44.7
	53.3	76.5	23.2
	57.1	79	21.9
Mean	**41.4**	**83.9**	**42.6**
SD	**24.6**	**8.2**	**27.3**
CFA (Mean, SD); Baseline CFA ≥ 60% (N=8)			
	60.5	98.6	38.1
	63.7	54.3	-9.4
	63.8	87.1	23.3
	65.8	84.1	18.3
	66.5	86.7	20.2
	68.9	98.3	29.4
	70.3	79.1	8.8
	71.4	92.5	21.1
Mean	**66.4**	**85.1**	**18.7**
SD	**3.7**	**14.2**	**14.2**

[1] Each patient is represented on each line.

The results for CFA at Baseline (no-treatment) and for CFA during Creon treatment for the ITT population are presented graphically in the following figure, Figure 5. The VISITN 1 column represents Baseline encounters and the VISITN 2 column represents encounters during Creon treatment. Each data point along the Y (RESULT) axis represents an individual patient's CFA reported in percent units. The bottom of each closed box delimits the lowest 25th percentile of CFA and the top of each box delimits the upper 75th percentile of CFA. The bottom line under each box delimits the lower 5th percentile of CFA and the topmost line above each box delimits the upper 95th percentile of CFA. The horizontal line within each box represents the median CFA for each treatment period. The dots below the boxes are outliers.

Figure 5: CFA at Baseline and During Creon Treatment in the ITT Population



RESULT: Coefficient of Fat Absorption (CFA) in %
VISITN: Baseline visit (1), treatment period visit (2)

As stated above efficacy will be determined by outcomes in the ITT population; however, this reviewer elected to evaluate change in CFA on the per protocol (PP) population to determine if there were clinically demonstrable differences in efficacy between the ITT and PP populations.

Mean Baseline CFA for the PP was 56% (SD=18.8), mean Treatment CFA was 85% (SD=13), and change in mean CFA was 29% (SD=23). Percentages are rounded to nearest whole number integer. These results are presented in Table 29 and Figure 6 below. Similar to CFA findings in the ITT population results are clinically meaningful, but no statistical inferences may be made.

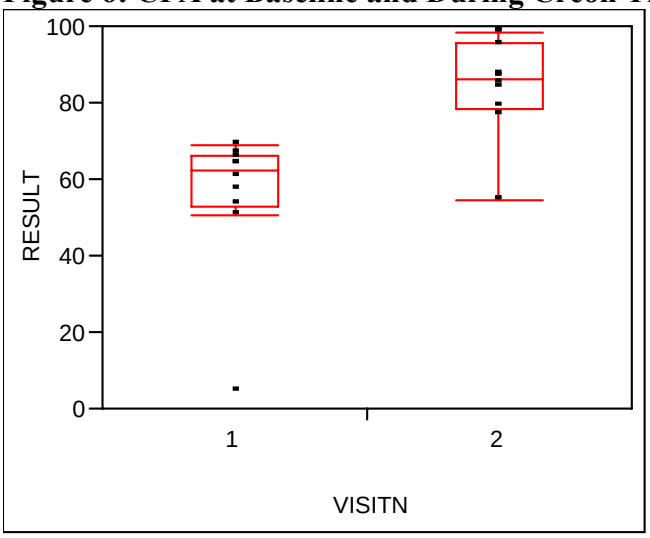
Table 29: New Infant CF Study: Individual Patient Change in CFA Treatment CFA minus Baseline CFA (Mean, SD); PP

PP population (N=10)			
	Baseline CFA	Treatment CFA	Change in CFA
	4.7	85.1	80.4
	50.3	95	44.7
	53.3	76.5	23.2
	57.1	79	21.9
	60.5	98.6	38.1
	63.7	54.3	-9.4
	63.8	87.1	23.3
	65.8	84.1	18.3
	66.5	86.7	20.2
	68.9	98.3	29.4
Mean	**55.5**	**84.5**	**29** [2]
SD	**18.8**	**13**	**23** [2]

[1] Each patient is represented on each line.

The results for CFA at Baseline (no-treatment) and for CFA during Creon treatment for the PP population are presented graphically in the following figure, Figure 6. The VISITN 1 column represents Baseline encounters and the VISITN 2 column represents encounters during Creon treatment. Each data point along the Y (RESULT) axis represents an individual patient's CFA reported in percent units. The bottom of each closed red boxes delimits the lowest 25th percentile of CFA and the top of each red box delimits the upper 75th percentile of CFA. The bottom red line under each box delimits the lower 5th percentile of CFA and the topmost red line above each box delimits the upper 95th percentile of CFA. The horizontal line within each box represents the median CFA for each treatment period.

Figure 6: CFA at Baseline and During Creon Treatment; PP Population



RESULT: Coefficient of Fat Absorption (CFA) in %
VISITN: Baseline visit (1), treatment period visit (2)

10.1.1.12.5.2 Secondary Efficacy Analysis

Secondary efficacy parameters were assessed by comparing changes in number of stools per day, body mass index (BMI), weight and height. Secondary efficacy analyses were not performed on the PP population.

No clinically or statistically meaningful changes were found in BMI or weight-for-height were demonstrated. Baseline measurements of BMI and Weight for Height indicate patients were not nutritionally deficient at time of enrollment which decreased the likelihood of detecting an effect on these two parameters. There was a slight decrease in number of stools per day which was not statistically significant. These findings are summarized in table 30 below. Individual patient results (+/- SD) are presented in Tables 31 (BMI), 32 (weight for height), and 33 (number of stools per day).

Table 30: New Infant CF Study 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: Statistical Reviewer's Analysis, from Table 13 page 48 and Table 16 on page 50 of the Sponsor's study report.
BMI= body Mass Index

Table 31: New Infant CF Study: Change in BMI; ITT (N=12)

BMI	Baseline	Visit 4 (week 8)	Change in BMI kg/m2
	15.3	16.2	0.9
	14.4	17.2	2.8
	16	16.8	0.9
	18.8	17.9	-0.9
	12.7	15.2	2.5
	14	15.8	1.8
	16.1	16.7	0.6
	14	14.3	0.3
	17.1	16.2	-0.9
	16.7	16.1	-0.6
	14.6	15.7	1.1
	17.1	17.4	0.3
Mean	**15.6**	**16.3**	**0.7**
SD	**1.7**	**1**	**1.2**

Table 32: New Infant CF Study: Change in Weight for Height; ITT (N=12)

Weight for Height	Baseline	Visit 4 (week 8)	Change Weight for Height
	99	111	12
	106	107	1
	97	105	8
	114	108	-6
	92	97	5
	86	95	9
	98	99	1
	81	86	5
	99	99	0
	95	95	0
	80	82	2
	115	102	-13
Mean	**96.8**	**98.8**	**2**
SD	**11.3**	**8.7**	**6.8**

There was a slight decrease in number of stools per day which was not statistically significant.

Table 33: New Infant CF Study: Change in Stools/Day; ITT (N=12)

Stools/day	Baseline	Week 8	Change in stool frequency
	4	4	0
	4	2	2
	3	3	0
	2	2	0
	3	0	3
	4	3	1
	4	3	1
	2	3	-1
	1	2	-1
	2	1	1
	2	2	0
	3	1	2
Mean	**2.8**	**2.1**	**0.7**
SD	**1**	**1.1**	**1.2**

Brief comment is made on several characteristics that were neither primary nor secondary efficacy measures. The sponsor reports all patients had steatorrhea on entry, seven patients had steatorrhea at visit four, mean stool weight decreased from 109 to 79 g/day, and mean dietary fat increased from 32 to 34.3 g/day. However, there was insufficient information in the DIARY, CLINSYMP, STOOL_D, GI_D datasets to permit analysis of mean stool weight or changes in dietary fat consumption.

The CLINSYMP dataset shows that two patients had moderate gastrointestinal symptoms (patient 2-1 at visit 1, and Patient 2-3 at visit 2) during treatment. All other entries for gastrointestinal symptoms are recorded as "none". In contradistinction the DIARY dataset indicates patients 1-9 and 2-3 had multiple episodes of "severe" and "none" gastrointestinal symptoms on multiple days. This incongruity was not resolved.

Conflicting data from datasets DIARY and CLINSYMP preclude comment on effect on gastrointestinal symptoms. The DIARY information was recorded by parent or caregiver. The CLINSYMP was recorded at scheduled visits by study investigators or designee.

Laboratory assessments are addressed under the Safety section of this review, 10.1.1.12.3.

10.1.1.12.6 Efficacy Summary

The primary endpoint was Treatment CFA minus Baseline CFA. The ITT population achieved A clinically meaningful increase in CFA was demonstrated in the ITT population (27%, SD=22; 95% C.I 12.9, 40.4). Due to the small size of the study, statistical inferences regarding significant could not be made. Likewise a clinically meaningful increase in CFA was demonstrated in the PP population (29%, SD=23) which also did not reach clinical significance.

Increase in mean CFA of the current study does not reach 30%. However, in four patients with Baseline CFA less than 60% mean increase in CFA was 43% (SD 27, 95% C.I. -0.9, 86.1). These findings are not statistically significant. Four of twelve patients in the ITT achieved pre-designated success with treatment period CFA > 90%; but again, no statistical inference can be drawn. There was no clinically meaningful effect on secondary efficacy parameters.

This reviewer concludes the overall results support clinically meaningful improvement in CFA in the population study with the doses provided.

The study was performed with the CMP. Due to lack of supportive data from the bridging study, primary efficacy trials must be done with the TbMP.

10.1.1.13 Review of Safety

10.1.1.13.1 Reports of Deaths and SAEs

No deaths were reported. No SAEs were reported. No more than six AEs were reported in any patient.

10.1.1.13.2 Treatment Emergent Adverse Events

Three AEs were reported in two patients during the Baseline period. One patient had malnutrition and cow's milk intolerance, and one patient had meteorism. There were 21 non-serious AEs reported during treatment with Creon MMS. The most common AEs by decreasing incidence in the population were pyrexia (33%), cough (25%), constipation (17%), and respiratory tract infections (17%). Conjunctivitis, abdominal pain NOS, viral infection NOS, nasopharyngitis, gastroenteritis adenovirus, rhinitis NOS, and pharyngeal pain each occurred in 8% of the study population. These findings are summarized in table 34 below.

Table 34: All Treatment Emergent AEs in the ITT; New Infant CF Study

		AEs	Patients Reporting AE	% Affected (N=12)
SOC	Preferred Term	Total N=21	N	
Eye Disorders	Conjunctivitis	1	1	8
Gastrointestinal Disorders	Constipation	3	2	17
	Abdominal Pain NOS	1	1	8
General Disorders and Administration Site Conditions	Pyrexia	4	4	33
Infections and Infestations	Viral Infection NOS	1	1	8
	Respiratory Tract Infection NOS	2	2	17
	Nasopharyngitis	3	1	8
	Gastroenteritis Adenovirus	1	1	8
Respiratory, Thoracic and Mediastinal Disorders	Rhinitis NOS	1	1	8
	Pharyngolaryngeal Pain	1	1	8
	Cough	3	3	25

These findings are similar to common complaints in healthy infants and infants with CF. The increased incidence of AEs during double blind treatment compared to the Baseline phase is likely due to the short Baseline period (seven to ten days) compared to the treatment period (eight weeks).

10.1.1.13.3 Vital signs

Vital sign data sets were reviewed and analyzed. Except for fevers recorded as AEs, there were no notable abnormal findings within in the treatment period compared to baseline.

10.1.1.13.4 Laboratory Analyses

Analyses of hematological and biochemical datasets for the ITT population were performed. Due to the small size of the study and the magnitude of change in laboratory parameters, results are presented descriptively (data not shown). Results are not statistically significant.

As expected, decreased concentrations of vitamins A and E were noted at Baseline. There was a slight increase in mean values of vitamins A and E during the study, but mean values remained either below normal or at the lower range of normal for these two analytes. However, clinically meaningful decreases in vitamin E levels were seen in two patients. Marked improvement in vitamins A and E would not be expected due to the short duration of the study.

Also, mean serum cholesterol increased by 0.27 millimol/L, which may be expected with increased lipid absorption with treatment and attendant increase in cholesterol biosynthesis.

10.1.1.14 Safety Summary

The most common AEs by MedDRA Preferred Term were pyrexia (33% affected), cough (25% affected), and constipation and respiratory tract infection (17% affected each). These AEs are similar to the AE profile of the ISS. These findings are similar to and not readily distinguishable from findings in the placebo group of the ISS.

No consistent clinically meaningful laboratory changes are noted.

10.1.1.15 Overall Summary of the New Infant CF Study (S248.3.003)

The study results support efficacy and short term safety in the population studied with the doses used in the trial.

10.1.2 New Adult PEI Study (S245.3.115)

The study was performed with a CMP formulation of MMS, rather than with the TbMP.

10.1.2.1 Study Design

This was a 12 to 13 day, randomized, double blind, parallel group, multi-center study to determine efficacy and safety of Creon MMS in adult patients with PEI due to CP and PY. After successful completion of screening, all patients received 5 days of placebo under single blind conditions, to establish a non-treatment run-in period. On completion of the single blinded placebo phase patients were randomized to receive seven days of treatment with either placebo, 1.5 gram/day (60,000 lipase U/day), or 3.0 gram/day (120,000 lipase U/day) of study drug for eight days under double-blind conditions. Stool collection for CFA was performed after at least 72 hours of single blind treatment (Baseline CFA) and after at least 72 hours of double-blinded treatment (drug or placebo; Treatment CFA). Patients were to maintain a diet containing at least 40 gram/day of dietary fat from immediately prior to study entry through the completion of double blinded treatment; however, this reviewer was unable to determine if patients were provided a standardized diet.

Primary efficacy was defined as the difference in mean Treatment CFA minus Baseline CFA between the low dose group and the placebo treated group, and between the high dose group and the placebo treated group.

Patients were to be at least 20 years old and had to have at least 7.5 g/day of stool fat at screening. The study was performed between 05-June-2000 and 23-June-2003. The ITT population consisted of ninety-four patients.

10.1.2.2 Study Objectives

Primary objectives were to determine efficacy and safety. The primary efficacy parameter the difference in mean Treatment CFA minus Baseline CFA between the low dose group and the placebo treated group and between the high dose group and the placebo treated group.

Secondary objectives were to determine if there were differences in mean Treatment CFA minus Baseline CFA between the low dose group and high dose group.

10.1.2.3 Eligibility Criteria

Patients were eligible for study participation if they were at least 20 years old, and had a diagnosis of either CP or PY with at least 7.5 g/day of stool fat at screening. Prior treatment with PEPs was allowed, but treatment must have ended no later than immediately prior to the beginning of the five-day placebo run-in phase.

Patients were excluded from study participation if their pre-study diet did not consist of at least 40 gram/day of dietary fat; if there was known clinically significant cardiovascular, gastrointestinal (other than primary disease), urogenital, or psychiatric/neurological disease; known allergy to the study drug or similar drug products; acute pancreatitis; superimposed acute pancreatitis, or if pregnant or lactating.

10.1.2.4 Concomitant and Prohibited Medications

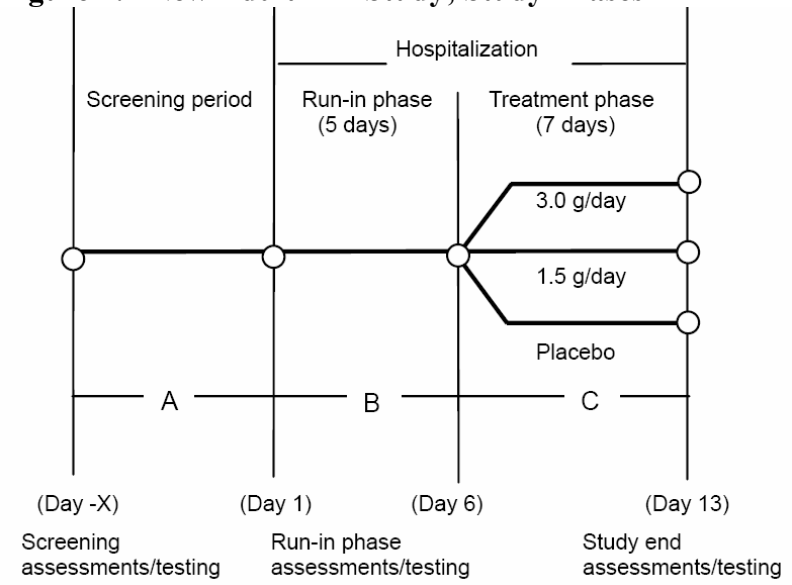
Medicines for pre-existing diseases (e.g., insulin for diabetes mellitus) were allowed. The following medicines were not allowed unless in already in use with a fixed dose at the time of screening: drugs affecting gastric or duodenal pH such as H2-antagonists, antacids and proton pump inhibitors; enhancers of gastric emptying such as erythromycin; antispasmodics, and antitrypsins. The preceding medicines could not be started after the study began.

Prohibited medicines included other digestive enzyme preparations, castor oil, oil cathartics, or oily suppositories during stool collection, and other investigational products.

10.1.2.5 Study Visits and Procedures

The study design and planned procedures are presented in Figure 7 and Table 35 below.

Figure 7: New Adult PEI Study; Study Phases



A: the screening period after obtaining informed consent until the study start
B: the 5-day placebo administration phase
C: the 7-day treatment phase with SA-001 3.0 g/day, 1.5 g/day, or placebo

Table 35: New Adult PEI Study Visits and Procedures

Assessment/testing item	Pre-study	Screening			Run-in phase (hospitalization)						Treatment phase (hospitalization)							
		1	2	3	1		2	3	4	5	6	7	8	9	10	11	12	13
Informed consent explanation	X																	
Informed consent		X																
Demographic and other baseline characteristics		X																
Patient registration (Drug allocation)					X													
Subjective complaint Objective symptom		X				X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration*						R*	R	R	R	R	R/T	T†	T	T	T	T	T	T
Dietary record						X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment compliance							X	X	X	X	X	X	X	X	X	X	X	X
Stool collection				X				<	▬	▬	>				<	▬	▬	>
Body height		X																
Body weight		X																
Blood pressure / Pulse rate		X									X							X
Laboratory tests [1]		X									X							X
Adverse events						X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Clinical laboratory evaluation (hematology, blood chemistry, and urinalysis) and stool fat determination, as well as sample retrieval after stool collection were made by contracted laboratory facilities.
* R: Administration of the study medication for the run-in phase, 3-times daily, except for Day 1 of the run-in phase (twice) and for Day 6 (once)
† T: Administration of the study medication for the treatment phase, 3-times daily, except for Day 6 (twice) and for Day 13 (once)
<▬>: Activity extends from (<), through (▬), to (>).

10.1.2.6 Randomization, Blinding and Controls

A third party study controller made drug-sets consisting of sets of placebo, 1.5 g/day Creon MMS, or 3.0 g/day Creon MMS doses, in random order. Two copies of a medication key-coded randomization table were kept at secure locations and remained unopened. Blinded review and data fixation preceded key-code opening. The study controller retained a code-key in case a medical situation arose necessitating emergent unblinding.

The first study phase was single blinded and the treatment phase was double blinded. The third party study controller corroborated the identity of administered substance (i.e., placebo, 1.5 gram per day dose, or 3.0 gram/day dose) and ensured distribution of correct study substance to correct patient. A designee of the controller assured post-study unidentifiability.

No emergency or pre-mature breakage of the code-key occurred.

10.1.2.7 Study Medication Dose Selection, Dispensing, and Compliance

10.1.2.7.1 Dose Selection

The doses that were studied were selected based on results of a unrelated phase II study of the same product in a similar study population, wherein fixed dosages at 3.0 or 6.0 grams/day, and titrated dosages (0.75, 1.5, and 3.0 gram/day) were administered. The Sponsor states that there was no significant improvement in CFA noted with 0.75 gram/day, that clinical effect with 1.5, 3.0 and 6.0 gram/day were "similar to each other", and there was "no clinically significant difference" in change in CFA between the 3.0 and 6.0 gram/day groups. The Sponsor's also states there was no relationship between adverse events and dose level. The investigators concluded it would be safe to conduct the current trial with placebo, 1.5 gram/day, and 3.0 ram per day dose groups and that there would be no expected benefit by studying 6.0 gram/day.

The study drug for the current study was designated SA-001 and is the same drug that was studied in the phase II study above (e.g., Creon MMS, CMP). The Sponsor states 1 gram of study drug contains 40,000 FIP lipase units, 32,200 amylase units, and 2,400 protease units

A conversion factor for lipase FIP units to lipase USP units is not provided.

10.1.2.7.2 Dispensing and Compliance

During the five day single-blind phase, all patients received placebo dispensed as 0.5 gram per sachets. During the double-blind treatment phase sachets contained either 0.5 gram of placebo or 0.5 gram of drug. Two sachets were provided for each meal. Patients in the placebo group received two 0.5 gram placebo sachets per meal, persons in the 1.5 gram/day group received one 0.5 gram placebo sachet and one 0.5 gram study drug sachet per meal. Patient in the 3 gram/day group received two 0.5 gram study drug sachets per meal.

Patients were hospitalized during the treatment phase. The investigator or their designee assessed compliance at the end of study, or on premature discontinuation by assessing the percentage of sachets consumed (almost all, >75%; forgot some, 50-74%; did not take at least half, not defined; did not take most, not defined; took sachets in too short a time period).

The Sponsor states compliance was 100%.

10.1.2.8 Efficacy and Endpoint Measures

The primary efficacy measure was Treatment CFA minus Baseline CFA.

The primary efficacy population was the ITT population (N=94). This reviewer also performed an efficacy analysis on the PY (N=59) and CP (N=35) sub-populations.

The sponsor also analyzed primary efficacy in the PP population (N=63).

10.1.2.8.1 Primary Efficacy Endpoints

Primary efficacy endpoint was change in CFA in each Creon treated group (low-dose or high dose) compared to change in CFA in the group that received placebo during the double-blind phase. First CFA must have been done after 72 hours of single-blinded placebo.

Efficacy determination was based solely on changes in CFA.

10.1.2.8.2 Secondary Efficacy Endpoint

Secondary efficacy parameters included changes in stool frequency, stool fat determination, and changes in daily calorie and fat intake.

Secondary efficacy endpoints were not used to establish efficacy.

10.1.2.8.3 Safety Assessments

Safety was assessed by type and incidence of AEs; discontinuations due to AEs; drug related serious, and severe AEs; changes in physical exam including vital signs, and clinical laboratory assessments, including clinical chemistry, hematology and urinalysis evaluations.

10.1.2.8.4 PK and PD Measures

Pancreatic enzyme replacement products act locally in the gastrointestinal tract and are not systemically absorbed. Traditional PK and PD measures were not performed as part of this study.

10.1.2.9 Additional Statistical Considerations

The primary efficacy analysis was constructed to compare efficacy of the 3.0 gram/day dose and the 1.5 gram/day dose compared to placebo, and to elicit any dose-response relationship with 1.5 and 3.0 gram/day doses.

Changes in % CFA are presented as continuous variables, and were summarized by minimum, median, and maximum reported % CFA value, arithmetic mean, standard deviation, and the number of CFA observations. Secondary outcomes (e.g., number of stools per day) were categorical variables and results were summarized absolute and relative frequencies.

10.1.2.10 Protocol Amendments

A list of protocol amendments is found in volume 48, page 17,545.

Two related amendments critical to review are now described. One amendment increased size of each treatment group from 18 to 25 patients. The Sponsor states this was done because a prior amendment allowed for a blinded, un-planned interim analysis suggested mean change in CFA and intra-group SD for the placebo group indicated that the original sample size was underpowered to demonstrate treatment effect. The blinded analysis was performed on the subset of patients who had at that time completed both the single-blind non-treatment phase and the double-blind (treatment or placebo) phase.

The Sponsor reports that the interim analysis suggested that the original sample size was underpowered to detect expected change in CFA between Creon treated groups compared to the placebo which were determined in a similar study, [16.6 (SD 17.4) for the low dose group] and [18.6 (SD 11.0) for the high dose group] with 13 patients per treatment group. Therefore, group size was increased from 18 to 25 patients per treatment arm to ensure a 90% power at a two sided significance level of 5%. The preceding information is detailed in volume 48 (pages 17,542 through 17,546) of the Sponsor's CR.

The Statistical reviewer, Dr. Sonia Castillo, concludes that since the interim analysis was not pre-specified and the potential effects on measures of statistical success were not provided, no statistical inferences can be made.

This reviewer concludes the efficacy findings of the New Adult PEI can not be used to support efficacy of Creon CMP for treatment of PEI due to PY or CP.

Another potentially significant stated that the statistical plan was amended prior to breaking the blind to provide for analyses using ANCOVA and ANOVA methods, and also to provide separate analyses for the pancreatectomy and chronic pancreatitis subgroups.

10.1.2.11 Study Conduct

The investigators state GCP was followed. Financial disclosure information was provided. No financial interests were reported.

10.1.2.12 Study Results

10.1.2.12.1 Patient Population and Demographics

Of 156 screened patients, 62 were excluded based on failed screening, withdrawal of consent, or pancreatic carcinoma. There were 94 patients in the ITT; 30 in the placebo group, 31 in the 1.5 gram/day group, and 33 in the 3.0 gram/day group. Thirty five patients had chronic pancreatitis and 59 had pancreatectomy. Gender distribution was unequal (81% men and 19% women). Patient age range was 26-83 years. Fifty patients had prior exposure to PEPs. Demographic information is provided in Table 36 below.

Table 36: New Adult PEI Study Demographic composition of the ITT

Parameter	Phenotype	Placebo	1.5 g/day	3.0 g/day	Total
		(N=30)	(N=31)	(N=33)	(N=94)
Sex (n [%])	Male	26 (87)	24 (77)	26 (79)	76 (81)
	Female	4 (13)	7 (23)	7 (21)	18 (19)
Age (years)	Mean (SD)	65.4 (10.2)	63.7 (9.2)	61.6 (12.4)	
Age (n [%])	21-30	-	-	1 (3)	1 (1)
	31-50	4 (13)	4 (13)	6 (18)	14 (15)
	51-64	8 (27)	8 (26)	11(33)	27 (29)
	65-	18 (60)	19 (61)	15 (46)	52 (55)
Height (cm)	Mean (SD)	161.2 (7.8)	161.2 (7.5)	161.3 (8.6)	
Height (n [%])	≤140	1 (3)	-	-	1 (1)
	141-150	1 (3)	4 (13)	4 (12)	9 (10)
	151-160	9 (30)	10 (32)	11 (33)	30 (32)
	161-170	18 (60)	16 (52)	14 (42)	48 (51)
	≥171	1 (3)	1 (3)	4 (12)	6 (6)
Weight (kg)	Mean (SD)	49.9 (6.2)	51.8 (10.5)	51.0 (8.2)	
Weight (n [%])	-30	1 (3)	-	1 (3)	2 (2)
	31-40	-	4 (13)	2 (6)	6 (6)
	41-50	14 (47)	11 (36)	13 (39)	38 (40)
	51-60	14 (47)	8 (26)	14 (42)	36 (38)
	61-	1 (3)	8 (26)	3 (9)	12 (13)
Diagnosis	Chronic Pancreatitis	12 (40)	11 (35)	12 (36)	35 (37)
	Pancreatectomy	18 (60)	20 (65)	21 (64)	59 (63)
Previous treatment	No	4 (13)	6 (19)	5 (15)	15 (16)
	Yes	26 (87)	25 (81)	28 (85)	79 (84)

10.1.2.12.2 Concomitant Medications

The Sponsor provides a list of all concomitant medicines administered to all patients. An analysis is not provided.

Medicines are listed by a combination of foreign and domestic trade name, drug class name, and generic name. Therefore, ability to perform substantive review is limited and results are presented descriptively.

The most frequently administered medicine classes were different forms of insulin (63% of patients in the placebo group, 45% in low dose, and 33% in high dose) and H-2 blockers (33% of patients in the placebo group, 29% in low dose, and 42% in the high dose group) most commonly famotidine (24% of all patients; 26 % in placebo group, 26% in the low dose group, and 30% in the high dose group).

Administration of anti-infectives was approximately even across treatment groups. Anti-infectives administered during the study included isoniazide (N=4 patients), rifampin (N=2), topical gentamicin-betamethasone (N=3), sulbactam-cefoperazone (N=2), ofloxacin (N=2), and N=1 each of cefaclor, cefotiam hydrochloride, cefpodoxime proxetil, chloramphenicol efradiomycin combined drug, clarithromycin, ketoconazole, clotrimazole, piperacillin sodium, imipenem-cilastatin, and bifonazole

Other commonly administered medicines administered during the study included anxiolytics (triazolam, N=10 patients; brotizolam, N=6; estazolam N=3; flunitrazepam, N=2 flunitrazepam; etizolam, N=2; and N=1 each of diazepam, quazepam, and nitrazepam); senna-base medicines (N=19), magnesium oxide (N=17), prokinetic agents (meospride, N=11 patients and metoclopramide N=4), ursodeoxycholic acid (N=13), camostat mesilate (N=12), and vitamin B-12 analogues (N=11).

There were no clinically meaningful differences in medications administered between treatment groups.

10.1.2.12.3 Compliance with Study Medications

Compliance was 100% by dose sachets per day. One patient took one dose sachet per each of 6 meals per day, rather than two dose sachets per each of three meals per day.

10.1.2.12.4 Protocol Deviations

Thirty-one patients were excluded from the ITT with a total of 40 reasons listed below

21 patients: insufficient stool fat excretion at end of run-in phase (<7.5 gram/day)
7 patients: incomplete stool collection at the end of the run-in phase (5 with no other exclusions
1 patient: unclear fat intake due to vomiting
1 patient: deviation from drug compliance rule
8 patients: insufficient fat intake, last 4 days of run-in or treatment phases (3 with no other exclusions)
2 patients: administration of prohibited medicines (also excluded for reasons above)

The most common protocol deviations are presented in table 37.

Table 37: New Adult PEI Study: List of Important Protocol Deviations

Deviation	Number of Patients with Deviation
Missing stool collections during run-in or treatment phases*	N=7 (Patients: 4-2, 7-3, 10-1, 16-3, 32-1, 40-2, and 45-3)
Change in dose regimen (see 10.1.2.14 above)*	N=1 (Patient 6-1)
Use of prohibited medications	N=7 (Patients 7-2*, 11-1, 12-1*, 16-1, 16-2, 25-1, 29-1)

Prohibited medications included: other enzyme preparations (1), newly prescribe anti-trypsin agent (1), change in dose of antacid (3), newly prescribed prokinetic agent.
* Excluded from per protocol set due to violations above. Patient 16-1 was excluded from the PPS due to < 7.5 gram/day stool fact excretion at end of run-in period.

This reviewer performed an efficacy analysis on the ITT (N=94). One patient was excluded from the low-dose group because there was no stool CFA during double-blind treatment.

10.1.2.12.5 Efficacy analysis

10.1.2.12.5.1 Primary Efficacy Analyses

The primary efficacy endpoint was change in CFA from the double-blind treatment phase (low dose or high dose Creon MMS (CMP), or placebo) minus CFA during single-blind (Baseline) placebo treatment (Treatment CFA minus Baseline CFA). The following efficacy comparisons were made: high-dose treatment group compared to placebo treated group, and low-dose treatment group compared to placebo treatment group.

Results for the primary efficacy endpoint, change in CFA from non-treatment (single-blind placebo) baseline phase compared to the DB (Creon or placebo treatment) phase for the ITT population, showed that change in mean CFA from baseline to DB treatment was 4% for the placebo group, 11% for the low-dose group, and 16% for the high-dose group. Compared to the placebo group, mean CFA change for the low-dose group was 7% (p-value = 0.144), and mean CFA change in the high-dose group was 12% (p-value = 0.015). The clinical meaning of these results is unclear due to an unplanned interim analysis discussed at the end of this section. This reviewer concludes these findings can not be used to support efficacy.

This reviewer also performed subgroup analyses of the primary endpoint for the PY and CP subgroups. For the CP subpopulation, change in mean CFA from baseline to DB treatment was 5% for the placebo group, 9% for the low-dose group and 7% for the high-dose group. Compared to the placebo group, mean CFA change for the low-dose group was 4% (p-value = 0.540), and mean CFA change in the high-dose group was 2% (p-value = 0.781). The clinical meaning of these results is unclear due to an unplanned interim analysis discussed at the end of this section. This reviewer concludes these findings can not be used to support efficacy.

For the PY subpopulation, change in mean CFA from baseline to DB treatment was 3% for the placebo group, 12% for the low-dose group and 20% for the high dose group. Compared to the placebo group, mean CFA change for the low-dose group was 9% (p-value = 0.180), and mean CFA change in the high-dose group was 18% (p-value = 0.011). The clinical meaning of these results is unclear due to an unplanned interim analysis discussed at the end of this section. This reviewer concludes these findings can not be used to support efficacy.

Most patients with Baseline (non-treatment) CFA less than 40%, and therefore capable of demonstrating greatest response, were in the high dose group of the PY sub-population, possibly accounting for the lack of response demonstrated in the CP sub-population and in the PY sub-population treated with low dose Creon CMP.

As discussed in Section 10.1.2.10 above, no statistical inferences can be made based on p-values due to inadequate description of the not pre-specified interim efficacy analysis.

Results of stool CFA analysis are presented in table 38 below. Individual patient baseline, treatment phase, and mean change in CFA are provided for review in tables 39 (ITT), 40 (CP subgroup), and 41 (PY subgroup) below.

Table 38: New Adult PEI Study: Change in Coefficient of Fat Absorption for All Patients by Diagnosis, ITT Population[1]

	Creon 1.5 g/day [3]	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.) [2]	7.1 (4.8)	11.6 (4.7)	
p-value for Mean Treatment Difference	0.144	0.015[4]	
Chronic Pancreatitis			
n	11	11	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[4]	

[1] Source: Statistical Reviewer's Analysis based on ANOVA model with treatment as factor.
[2] Standard Error
[3] One patient included in the FAS in the 1.5 g/day group did not have treatment period CFA performed/recorded thereby reducing n from 31 to 30 patients.
[4] No statistical inferences can be made based on p-values due to inadequate description of an interim efficacy analysis

Table 39: New Adult PEI: Coefficient of Fat Absorption (Mean, SD), ITT Population[1]

	Placebo			Low Dose			High Dose		
	Baseline	**Treatment**	**Change**	**Baseline**	**Treatment**	**Change**	**Baseline**	**Treatment**	**Change**
	WD	--	--	27.1	68.6	41.5	14.7	88.3	73.6
	3.6	-7.8	-11.4	37.7	74.2	36.5	18.3	87.7	69.4
	13.8	43.5	29.7	40	52.2	12.2	20.5	65.1	44.6
	19.1	63.5	44.4	44.1	10.4	-33.7	20.6	65.5	44.9
	23.1	64.7	41.6	51.2	83.8	32.6	30.6	86.6	56
	35.1	45.9	10.8	52.3	92.9	40.6	40	77.4	37.4
	36.3	40.4	4.1	52.9	X	X	52.3	81.3	29
	37.4	54.2	16.8	53.4	82.2	28.8	55.9	55	-0.9
	41.1	55.6	14.5	54.9	64	9.1	60.5	65	4.5
	43.9	64.6	20.7	54.9	74.1	19.2	62.5	81.5	19
	45.2	37.6	-7.6	54.9	86.5	31.6	68.2	87.2	19
	45.4	44.4	-1	57	75.1	18.1	68.1	90.1	22
	49.8	52	2.2	59.4	85.1	25.7	68.9	78.6	9.7
	50.2	41.7	-8.5	59.7	61.1	1.4	69.1	87.7	18.6
	51.6	45.1	-6.5	60.1	81.1	21	70.9	83.7	12.8
	52.8	60.1	7.3	65	80.5	15.5	71.2	90.5	19.3
	54.3	63.9	9.6	66.8	70.9	4.1	73	60.7	-12.3
	54.5	51.3	-3.2	68	48.6	-19.4	76.3	89.1	12.8
	57.7	43.6	-14.1	68.9	82	13.1	78.1	64.8	-13.3
	60.6	61.9	1.3	69.1	87.1	18	81.9	78.8	-3.1
	61	58.5	-2.5	69.3	91	21.7	82.7	97.5	14.8
	63.7	75.7	12	83	79.4	-3.6	84.2	92.4	8.2
	63.9	73.1	9.2	84.1	86.5	2.4	85.9	76.2	-9.7
	66.8	57.2	-9.6	86.7	88.6	1.9	86.2	85.6	-0.6
	83.8	74.5	-9.3	86.8	90.4	3.6	86.3	94.7	8.4
	83.8	87.9	4.1	87.3	76.3	-11	86.3	92.8	6.5
	85.6	71.1	-14.5	91.6	91.2	-0.4	86.7	93.8	7.1
	88.7	88.8	0.1	96	96.9	0.9	87.9	89.2	1.3
	89.6	70.7	-18.9	96	97.1	1.1	87.9	94.9	7
	89.4	85.3	-4.1	96.9	93.4	-3.5	88.8	96.9	8.1
	92.2	90.8	-1.4	94.7	93.3	-1.4	89.7	93	3.3
Mean	**54.8**	**58.7**	**3.9**	**66.8**	**78.2**	**10.9**	91.2	93.4	2.2
SD	**23.6**	**19.8**	**15.4**	**19.1**	**17.8**	**17.6**	95.6	87.3	-8.3
							Mean	**67.9**	**83.4**	**15.5**
							SD	**23.7**	**11.4**	**21.8**

Baseline: CFA during single blind placebo treatment phase
Treatment: CFA during double-blind treatment phase
Change: CFA Treatment minus CFA Baseline
X: CFA data not located; addressed in Statistician's separate analysis
WD: Patient withdrew consent after randomization but prior to single-blind treatment.

Table 40: New Adult PEI: Coefficient of Fat Absorption (Mean, SD), CP sub-population, ITT

	Placebo				Low Dose				High Dose		
	Baseline	**Treatment**	**Change**		**Baseline**	**Treatment**	**Change**		**Baseline**	**Treatment**	**Change**
	23.1	64.7	41.6		54.9	74.1	19.2		40	77.4	37.4
	37.4	54.2	16.8		59.4	85.1	25.7		55.9	55	-0.9
	41.1	55.6	14.5		59.7	61.1	1.4		68.2	87.2	19
	43.9	64.6	20.7		60.1	81.1	21		76.3	89.1	12.8
	45.2	37.6	-7.6		65	80.5	15.5		78.1	64.8	-13.3
	45.4	44.4	-1		68	48.6	-19.4		86.2	85.6	-0.6
	51.6	45.1	-6.5		68.9	82	13.1		86.3	94.7	8.4
	61	58.5	-2.5		69.1	87.1	18		86.7	93.8	7.1
	66.8	57.2	-9.6		86.7	88.6	1.9		87.9	89.2	1.3
	83.8	87.9	4.1		91.6	91.2	-0.4		87.9	94.9	7
	89.4	85.3	-4.1		84.1	86.5	2.4		89.7	93	3.3
	92.2	90.8	-1.4	**Mean**	**69.8**	**78.7**	**8.9**		91.2	93.4	2.2
Mean	**56.7**	**62.2**	**5.4**	**SD**	**12.3**	**12.9**	**13.1**	**Mean**	**77.9**	**84.8**	**6.9**
SD	**22.1**	**17.5**	**15.2**					**SD**	**15.8**	**12.8**	**12.5**

Baseline: CFA during single blind placebo treatment phase
Treatment: CFA during double-blind treatment phase
Change: CFA Treatment minus CFA Baseline

Table 41: New Adult PEI: Coefficient of Fat Absorption (Mean, SD), PY sub-population, ITT

	Placebo				Low Dose				High Dose		
	Baseline	**Treatment**	**Change**		**Baseline**	**Treatment**	**Baseline**		**Change**	**Treatment**	**Baseline**
	3.6	-7.8	-11.4		27.1	68.6	41.5		14.7	88.3	73.6
	13.8	43.5	29.7		37.7	74.2	36.5		18.3	87.7	69.4
	19.1	63.5	44.4		40	52.2	12.2		20.5	65.1	44.6
	35.1	45.9	10.8		44.1	10.4	-33.7		20.6	65.5	44.9
	36.3	40.4	4.1		51.2	83.8	32.6		30.6	86.6	56
	49.8	52	2.2		52.3	92.9	40.6		52.3	81.3	29
	50.2	41.7	-8.5		52.9	X	X		60.5	65	4.5
	52.8	60.1	7.3		53.4	82.2	28.8		62.5	81.5	19
	54.3	63.9	9.6		54.9	64	9.1		68.1	90.1	22
	54.5	51.3	-3.2		54.9	86.5	31.6		68.9	78.6	9.7
	57.7	43.6	-14.1		57	75.1	18.1		69.1	87.7	18.6
	60.6	61.9	1.3		66.8	70.9	4.1		70.9	83.7	12.8
	63.7	75.7	12		69.3	91	21.7		71.2	90.5	19.3
	63.9	73.1	9.2		83	79.4	-3.6		73	60.7	-12.3
	83.8	74.5	-9.3		87.3	76.3	-11		81.9	78.8	-3.1
	85.6	71.1	-14.5		86.8	90.4	3.6		82.7	97.5	14.8
	88.7	88.8	0.1		94.7	93.3	-1.4		84.2	92.4	8.2
	89.6	70.7	-18.9		96	96.9	0.9		85.9	76.2	-9.7
Mean	49.5	56.3	2.8		96	97.1	1.1		86.3	92.8	6.5
SD	30.1	21.3	15.9		96.9	93.4	-3.5		88.8	96.9	8.1
				Mean	65.2	77.8	12.1		95.6	87.3	-8.3
				SD	22.1	20.4	19.9	Mean	62.2	82.6	20.4
								SD	25.9	10.8	24.6

Baseline: CFA during single blind placebo treatment phase
Treatment: CFA during double-blind treatment phase
Change: CFA Treatment minus CFA Baseline
X: CFA data not located; addressed in Statistician's separate analysis

The Sponsor also performed an efficacy analysis on the PP population which excluded 31 patients discussed in section 10.1.2.12.4 above. There is no statistically significant change in CFA in the PP population, or the PY or CP sub-populations. Results are summarized below.

For the entire PP population, mean change in CFA from Baseline to double-blinded treatment was +8% for the placebo group, +15% for the low dose group, and 20% for the high dose group. Mean CFA change compared to the placebo group in the low-dose group was 6% (p-value = 0.332), and was 12% (p-value = 0.055) for the high dose group.

For the CP sub-population of the PP population mean change in CFA from Baseline to double-blinded treatment was 9% for the placebo group, +10% for the low dose group and 12% for the high dose group. Mean CFA change compared to the placebo group was for the low-dose group was 2% (p-value = 0.843), and was 3% (p-value = 0.710) for the high dose group.

For the PY sub-population of the PP population mean change in CFA from Baseline to double-blinded treatment was +8% for the placebo group, +18% for the low dose group and +24 for the high dose group. Mean CFA change compared to the placebo group for the low dose group was 9 % (p-value = 0.322), and was 15% (p-value = 0.086) for the high dose group. The primary efficacy findings for the PP population are presented in Table 42 below. Individual patient baseline, treatment phase, and mean change in CFA are provided for review in Tables 43 (PP), 44 (CP subgroup), and 45 (PY subgroup) below.

Table 42: New Adult PEI Study: Change in CFA (%) for All Patients and by Diagnosis for Per Protocol Population[1]

	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.) [2]	6.2 (6.4)	12.0	
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	

[1] Source: Statistical Reviewer's Analysis based on ANOVA model with treatment as factor.
[2] Standard Error
[3] No statistical inferences can be made based on p-values due to inadequate description of an interim efficacy analysis

Table 43: New Adult PEI: Coefficient of Fat Absorption (Mean, SD), PP Population[1]

	Placebo			Low Dose			High Dose		
	Baseline	**Treatment**	**Change**	**Baseline**	**Treatment**	**Baseline**	**Change**	**Treatment**	**Baseline**
	3.6	-7.8	-11	27.1	68.6	41.5	14.7	88.3	73.6
	13.8	43.5	29.7	37.7	74.2	36.5	18.3	87.7	69.4
	19.1	63.5	44.4	40	52.2	12.2	20.5	65.1	44.6
	23.1	64.7	41.6	44.1	10.4	-33.7	20.6	65.5	44.9
	36.3	40.4	4.1	51.2	83.8	32.6	30.6	86.6	56
	37.4	54.2	16.8	52.3	92.9	40.6	40	77.4	37.4
	41.1	55.6	14.5	54.9	86.5	31.6	52.3	81.3	29
	43.9	64.6	20.7	54.9	74.1	19.2	55.9	55	-0.9
	45.4	44.4	-1	54.9	64	9.1	60.5	65	4.5
	49.8	52	2.2	57	75.1	18.1	68.1	90.1	22
	50.2	41.7	-8.5	59.4	85.1	25.7	68.2	87.2	19
	51.6	45.1	-6.5	59.7	61.1	1.4	69.1	87.7	18.6
	54.3	63.9	9.6	60.1	81.1	21	70.9	83.7	12.8
	54.5	51.3	-3.2	66.8	70.9	4.1	71.2	90.5	19.3
	60.6	61.9	1.3	68	48.6	-19.4	73	60.7	-12.3
	61	58.5	-2.5	68.9	82	13.1	81.9	78.8	-3.1
	63.7	75.7	12	69.1	87.1	18	82.7	97.5	14.8
	63.9	73.1	9.2	69.3	91	21.7	84.2	92.4	8.2
	66.8	57.2	-9.6	83	79.4	-3.6	85.9	76.2	-9.7
	83.8	87.9	4.1	84.1	86.5	2.4	86.2	85.6	-0.6
Mean	**46.2**	**54.6**	**8.4**	**58.1**	**72.7**	**14.6**	86.3	94.7	8.4
SD	**19.8**	**19.1**	**15.9**	**14.2**	**19.1**	**19.3**	86.3	92.8	6.5
							86.7	93.8	7.1
							Mean	**61.5**	**81.9**	**20.4**
							SD	**25.1**	**12**	**23.8**

Baseline: CFA during single blind placebo treatment phase
Treatment: CFA during double-blind treatment phase
Change: CFA Treatment minus CFA Baseline

Table 44: New Adult PEI: Coefficient of Fat Absorption (Mean, SD), CP sub-population PP

	Placebo				Low Dose				High Dose		
	Baseline	**Treatment**	**Baseline**		**Baseline**	**Treatment**	**Baseline**		**Baseline**	**Treatment**	**Baseline**
	23.1	64.7	41.6		54.9	74.1	19.2		40	77.4	37.4
	37.4	54.2	16.8		59.4	85.1	25.7		55.9	55	-0.9
	41.1	55.6	14.5		59.7	61.1	1.4		68.2	87.2	19
	43.9	64.6	20.7		60.1	81.1	21		86.2	85.6	-0.6
	45.4	44.4	-1		68	48.6	-19.4		86.3	94.7	8.4
	51.6	45.1	-6.5		68.9	82	13.1		86.7	93.8	7.1
	61	58.5	-2.5		69.1	87.1	18	**Mean**	**70.6**	**82.3**	**11.7**
	66.8	57.2	-9.6		84.1	86.5	2.4	**SD**	**19.5**	**14.8**	**14.5**
	83.8	87.9	4.1	**Mean**	**65.5**	**75.7**	**10.2**				
Mean	**50.5**	**59.1**	**8.7**	**SD**	**9.2**	**13.9**	**14.7**				
SD	**17.9**	**13**	**16.3**								

Baseline: CFA during single blind placebo treatment phase
Treatment: CFA during double-blind treatment phase
Change: CFA Treatment minus CFA Baseline

Table 45: New Adult PEI: Coefficient of Fat Absorption (Mean, SD), PY sub-population PP

	Placebo				Low Dose				High Dose		
	Baseline	**Treatment**	**Baseline**		**Baseline**	**Treatment**	**Baseline**		**Baseline**	**Treatment**	**Baseline**
	3.6	-7.8	-11.4		27.1	68.6	41.5		14.7	88.3	73.6
	13.8	43.5	29.7		37.7	74.2	36.5		18.3	87.7	69.4
	19.1	63.5	44.4		40	52.2	12.2		20.5	65.1	44.6
	36.3	40.4	4.1		44.1	10.4	-33.7		20.6	65.5	44.9
	49.8	52	2.2		51.2	83.8	32.6		30.6	86.6	56
	50.2	41.7	-8.5		52.3	92.9	40.6		52.3	81.3	29
	54.3	63.9	9.6		54.9	64	9.1		60.5	65	4.5
	54.5	51.3	-3.2		54.9	86.5	31.6		68.1	90.1	22
	60.6	61.9	1.3		57	75.1	18.1		69.1	87.7	18.6
	63.7	75.7	12		66.8	70.9	4.1		70.9	83.7	12.8
	63.9	73.1	9.2		69.3	91	21.7		71.2	90.5	19.3
Mean	**42.7**	**50.8**	**8.1**		83	79.4	-3.6		73	60.7	-12.3
SD	**21.3**	**22.9**	**16.4**	**Mean**	**53.2**	**70.8**	**17.6**		81.9	78.8	-3.1
				SD	**15.2**	**22.3**	**21.9**		82.7	97.5	14.8
									84.2	92.4	8.2
									85.9	76.2	-9.7
									86.3	92.8	6.5
								Mean	**58.3**	**81.8**	**23.5**
								SD	**26.6**	**11.4**	**26**

Baseline: CFA during single blind placebo treatment phase
Treatment: CFA during double-blind treatment phase
Change: CFA Treatment minus CFA Baseline

10.1.2.12.5.2 Secondary Efficacy Analyses

Efficacy determination was based solely on primary efficacy parameters.

Secondary efficacy parameters were descriptive. Secondary efficacy parameters were assessed for the ITT population and the PY and CP sub-populations. Secondary efficacy parameters were not assessed for the PP population or its sub-populations.

Results of stool frequency are presented in Table 46 below. There was no clinically or statistically meaningful change in stool frequency in the ITT population or either the PY or the CP sub-populations.

Table 46: New Adult PEI Study: Change in Stools per Day for All Patients by Diagnosis, ITT Population[1]

	Creon 1.5 g/day [3]	Creon 3 g/day	Placebo
Overall			
n	30	33	30
Baseline mean	6.0	5.5	7.1
Mean change from baseline	-0.23	-0.33	-0.20
Mean Treatment Difference vs. Placebo (s.e.) [2]	-0.03 (0.59)	-0.13 (0.58)	
p-value for Mean Treatment Difference	0.955	0.819	
Chronic Pancreatitis			
n	11	12	12
Baseline mean	5.8	6.2	6.9
Mean change from baseline	-0.36	0.08	-1.25
Mean Treatment Difference vs. Placebo (s.e.)	0.89 (1.00)	1.33 (0.98)	
p-value for Mean Treatment Difference	0.382	0.182	
Pancreatectomy			
n	19	21	18
Baseline mean	6.1	5.2	7.2
Mean change from baseline	-0.16	-0.57	0.50
Mean Treatment Difference vs. Placebo (s.e.)	-0.66 (0.72)	-1.07 (0.71)	
p-value for Mean Treatment Difference	0.367	0.135	

[1] Source: Statistical Reviewer's Analysis based on ANOVA model with treatment as factor.
[2] Standard Error
[3] One patient included in the FAS in the 1.5 g/day group did not have treatment period CFA performed/recorded thereby reducing n from 31 to 30 patients.

Results of changes in caloric intake are presented in Table 47 below. There was no clinically or statistically meaningful change in stool frequency in the ITT population or either the PY or the CP sub-populations. This reviewer notes that diet was not controlled and that assessment of caloric intake was based on patient/care-giver diary reports.

Table 47: New Adult PEI Study: Change in Caloric Intake (kcal/day) for All Patients by Diagnosis, ITT Population[1]

	Creon 1.5 g/day[3]	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.)[2]	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	

[1] Source: Statistical Reviewer's Analysis based on ANOVA model with treatment as factor.
[2] Standard Error
[3] One patient included in the FAS in the 1.5 g/day group did not have treatment period CFA performed/recorded thereby reducing n from 31 to 30 patients.

10.1.2.12.6 Efficacy Summary

The New Adult PEI study evaluated change in CFA from non-treatment (SB placebo) phase to DB treatment (Creon or placebo) phase in adults with PEI due to CP or PY. Compared to the placebo group, the mean CFA change for the low-dose group was 7% (p-value = 0.144), and mean CFA change for the high dose group was 12% (p-value = 0.015). In the PY sub-population, mean increase in CFA for the high-dose group compared to placebo was 18 (p-value - 0.011). Efficacy was not demonstrated in CP patients treated with either low dose or high dose Creon CMP. Most patients with Baseline (non-treatment) CFA less than 40%, and therefore capable of demonstrating greatest response, were in the high dose group of the PY sub-population, possibly accounting for the lack of response demonstrated in the CP sub-population and in the PY sub-population treated with low dose Creon CMP.

The Sponsor performed a non pre-specified interim analysis which suggested that the original study was underpowered to detect the expected change in CFA between the Creon-treated groups compared to the placebo group. Therefore, group size was increased from 18 to 25 patients per treatment arm to ensure a 90% power at a two-sided significance level of 5%. The Statistical Reviewer, Dr. Sonia Castillo, concludes that since the interim analysis was not pre-specified and the potential effects on

measures of statistical success were not provided, no statistical inferences of the efficacy results can be made.

Thus, it is the assessment of this Reviewer that the clinical findings of the New Adult PEI do not support the efficacy of Creon CMP for treatment adult patients with PEI due to PY or CP

Also, the study was performed with the CMP. Due to lack of supportive data from the bridging study, primary efficacy trials must be done with the TbMP.

10.1.2.13 Review of Safety

10.1.2.13.1 Reports of Deaths and SAEs

No treatment emergent deaths were reported.

Three patients experienced SAEs in the single-blind placebo phase (Baseline) including hypoglycemia (N=2 patients), and edema NOS (N=1). Four patients experienced SAEs during the treatment phase. Three patients in the placebo group experienced one SAE each, including pyrexia; subdural hematoma, and hypoglycemia. One patient in the 3 gram/day group experienced pyrexia. No SAE was judged to be related to study drug. No SAE was associated with patient withdrawal from the study. These findings are summarized in Table 48 below.

Table 48: New Adult PEI Study: Treatment Emergent SAEs

SOC term	Preferred Term	N Events	Placebo	1.5g	3.0g
General disorders and administration site conditions	Pyrexia	2	1	0	1
Metabolism and nutrition disorders	Hypoglycemia NOS	1	1	0	0
Nervous system disorders	Subdural hematoma	1	1	0	0

10.1.2.13.2 Treatment Emergent Adverse Events (TEAE)

Forty five patients experienced between 1 and 13 non-serious AEs during the placebo run-in period. The most common AEs during the placebo run-in period were diarrhea (9% patients), hypoglycemia (7%), and abdominal distension, loose stools, and abnormalities of alanine aminotransferase and aspartic acid aminotransferase (5% each). AEs during the placebo run-in period were less common in the group randomized to receive placebo during double blind treatment (40% of patients in the placebo group, 52% of patients the low dose group, and 52% of patients in the high dose group). Results are summarized in Table 49 below.

Treatment 49: New Adult PEI Study: AEs occuring in ≥ 3% patients during single-blind placebo phase

Total Patients by Treatment		Total (N=94)		1.5 g/day (N=31)		3 g/day (N=33)		Placebo (N=30)	
SOC	Preferred Term	n	%	n	%	n	%	n	%
Gastrointestinal disorders	Diarrhea NOS	8	9	4	13	3	9	1	3
	Abdominal distension	5	5	2	7	3	9	0	0
	Loose stools	5	5	1	3	2	6	2	7
	Abdominal pain NOS	4	4	2	7	1	3	1	3
	Constipation	3	3	3	10	0	0	0	0
General disorders and administration site conditions	Pyrexia	3	3	1	3	1	3	1	3
Investigations	Alanine aminotransferase increased	5	5	1	3	3	9	1	3
	Aspartate aminotransferase increased	5	5	1	3	3	9	1	3
	Blood cholesterol decreased	4	4	0	0	3	9	1	3
	Blood albumin decreased	3	3	0	0	2	6	1	3
	Blood glucose decreased	3	3	0	0	1	3	2	7
	Gamma-glutamyltransferase increased	3	3	2	7	1	3	0	0
	High density lipoprotein decreased	3	3	0	0	2	6	1	3
	Protein total decreased	3	3	0	0	2	6	1	3
	Platelet count decreased	2	2	0	0	2	6	0	0
Metabolism and nutrition disorders	Hypoglycemia NOS	7	7	1	3	3	9	3	10
Musculoskeletal and connective tissue disorders	Arthralgia	3	3	0	0	2	6	1	3

n: number of patients experiencing an event one or more times

There were 158 AEs in 64 patients during double-blind treatment (see Table 50 below). AEs were reported in 63% of patients in the placebo group, 70% of patients in the high-dose group, and 74% of patients in the low-dose group. The most common AEs across all treatment groups were abdominal pain (10%), constipation (9%), and abdominal distension, diarrhea and malaise (7% each). Review of the study report, CRFs, and datasets does not provide any rationale why AEs were less common in the placebo treated group. However, it is noted the group randomized to receive placebo during the double blind period had a similarly lower incidence of AE during the baseline phase.

The most common AEs in the placebo group were malaise (14%), abdominal pain, abdominal distension, and hypoglycemia (10% each). The most common AEs in the low dose group were abdominal pain, back pain, and headache (10% each). The most common AEs in the high dose group were constipation and diarrhea (15% each), followed by abdominal pain, vomiting, and gastrointestinal upset (9% each).

Table 50 lists all treatment emergent AEs occuring in > 3% of patients.

Table 50: New Adult PEI Study, AEs reported ≥ 3 patients, by treatment group

All patients by treatment		Total (N=94)			1.5 g/day (N=31)			3 g/day (N=33)			Placebo (N=30)		
		AEs	N	%	AE	N	%	AE	N	%	AE	N	%
		158	65	69	41	23	74	63	23	70	54	19	63
Listing of Individual AEs													
SOC	Preferred Term	AEs	N	%	AE	N	%	AE	N	%	AE	N	%
Gastrointestinal disorders	Abdominal pain NOS	9	9	10	3	3	10	3	3	9	3	3	10
	Abdominal distension	8	7	7	3	2	7	2	2	6	3	3	10
	Constipation	8	8	9	1	1	3	5	5	15	2	2	7
	Diarrhea NOS	7	7	7	0	0	0	5	5	15	2	2	7
	Loose stools	6	6	6	2	2	7	2	2	6	2	2	7
	Vomiting NOS	4	4	4	1	1	3	3	3	9	0	0	0
	Gastrointestinal upset	3	3	3	0	0	0	3	3	9	0	0	0
General disorders and administration site conditions	Malaise	7	7	7	1	1	3	2	2	6	4	4	13
	Chest discomfort	3	3	3	0	0	0	1	1	3	2	2	7
Investigations	Blood glucose increased	6	6	6	1	1	3	3	3	9	2	2	7
	Glucose urine present	3	3	3	2	2	7	0	0	0	1	1	3
Metabolism and nutrition disorders	Hypoglycemia NOS	4	4	4	0	0	0	1	1	3	3	3	10
Musculoskeletal and connective tissue disorders	Back pain	4	4	4	3	3	10	1	1	3	0	0	0
Nervous system disorders	Headache	4	4	4	3	3	10	1	1	3	0	0	0
	Dizziness	3	3	3	0	0	0	1	1	3	2	2	7
Skin and subcutaneous tissue disorders	Cold sweat	3	3	3	0	0	0	2	2	6	1	1	3
	Pruritus	3	3	3	2	2	7	0	0	0	1	1	3

Adverse events were classified as treatment related if the relationship of the event to treatment) was classified as possible, probable, highly probable, or unknown. Treatment related events were reported in the placebo (N=13), low dose (N=8), and high dose (N=21) groups. In depth review of the datasets and accompanying CRFs found no apparent difference in the occurrence of moderate and severe non-serious AEs (8 events in 3 patients in the placebo group; five events in four patients in the low-dose group; and six events in four patients in the high-dose group). No moderate or severe AE was related to drug administration. (Data not shown)

This reviewer concludes AEs in the placebo and treatment group reflect underlying pathophysiology, and that treatment of Adult patients with PEI due to PY and CP with Creon MMS does not increase risk of AEs. This safety information is adequate to inform labeling of Creon MMS (CMP) in patients with PEI due to PY and CP.

10.1.2.13.3 Laboratory Analyses

The laboratory datasets were reviewed in depth. The most common biochemical abnormality was hyperglycemia. Sixty-one of 94 patients had one or more recorded episodes of hyperglycemia or

hypoglycemia. Ten of 11 patients changes in blood glucose classified as clinically relevant by the Sponsor had hyperglycemia one or more times. All ten of these patients had pre-existing diagnoses of diabetes mellitus.

Ninety-three of 94 patients had one or more abnormal urine parameters on one or more urinalyses. Glucosuria was the most common treatment phase urine abnormality. All patients with more than "+/-" glucosuria had hyperglycemia and pre-enrollment diagnosis of diabetes mellitus. There were no clinically meaningful trends in other urine parameters within or across treatment groups.

No clinically meaningful changes were seen in hematologic parameters (see table 51, below).

Table 51: Hematologic characteristics, Mean (SD) for all treatment groups, ITT

Laboratory Parameter	Phase	Placebo		Low Dose		High Dose	
		Mean	SD	Mean	SD	Mean	SD
WBC	Baseline	6,010	2,115	5,484	1,934	5,968	2,093
	Treatment	5,748	1,816	5,650	1,979	6,450	2,093
	Change	-262	1,323	240	1004	375	2,225
RBC	Baseline	376	62	389	57	400	50
	Treatment	375	55	383	62	396	64
	Change	-1.6	20.3	-0.5	20	1.9	28.6
Hemoglobin	Baseline	11.7	1.9	12.1	1.7	12.5	1.7
	Treatment	11.7	1.7	11.9	1.9	12.4	2.1
	Change	-0.0	0.7	-0.1	0.7	0.1	0.9
Hematocrit	Baseline	35.4	5.3	36.2	4.8	37.6	4.8
	Treatment	35.0	4.9	35.6	5.3	37.2	6.0
	Change	-0.3	1.9	-0.2	1.9	0.175	2.8
Platelet	Baseline	239.9	94.9	218.9	57.8	187.0	59.0
	Treatment	211.1	86.8	202.4	59.4	199.6	61.6
	Change	-18.2	27.0	-8.9	24.1	7.9	24.4

No clinically meaningful changes were seen in lipid parameters, or uric acid. Mean Baseline and Treatment period blood glucose values were above normal for all groups. The results are summarized in table 52, below.

Table 52: New Adult PEI Study: Triglycerides, Total cholesterol, HDL Cholesterol, Blood Glucose, and Uric acid for all treatment groups, ITT

Laboratory Parameter	Phase	Placebo		1.5 gram/day		3.0 gram/day	
		Mean	SD	Mean	SD	Mean	SD
Triglycerides	Baseline	79	35	99	54	84	43
	Treatment	75	33	94	47	90	51
	Change	-4	19	-5	24	6	31
Total Cholesterol	Baseline	137	38	146	40	144	43
	Treatment	133	41	157	43	159	42
	Change	-4	17	10	18	15	22
HDL Cholesterol	Baseline	47	15	45	11	47	18
	Treatment	48	16	49	15	50	20
	Change	0.3	7	4	8	3	7
Glucose	Baseline	115	56	128	51	126	55
	Treatment	154	90	136	58	138	52
	Change	39	64	8	33	12	49
Uric Acid	Baseline	5.2	1.6	5.1	1.5	4.8	1.6
	Treatment	5.0	1.5	4.7	1.6	4.8	1.6
	Change	-0.2	0.5	-0.4	0.7	-0.1	0.7

10.1.2.13.4 Vital Signs

Vital sign data sets were reviewed and analyzed. There were no clinically meaningful trends seen within or between treatment groups compared to baseline. These results are summarized in table 53 below.

Table 53: New Adult PEI Study: Vital Signs (Mean, SD)

Vital sign parameter	Phase	Placebo		Low Dose		High Dose	
		Mean	SD	Mean	SD	Mean	SD
Systolic blood pressure (mmHg)	Baseline	116.2	19.0	114.8	16.1	119.0	17.8
	Treatment	119.4	17.3	115.3	19.3	122.6	18.6
	Change	3.2	14.7	0.5	11.7	3.6	16.6
Diastolic blood pressure (mmHg)	Baseline	69.8	9.7	69.0	9.9	69.0	11.5
	Treatment	71.1	8.5	68.4	9.4	70.5	10.0
	Change	1.3	10.6	-0.6	8.9	1.5	10.2
Pulse rate (bpm)	Baseline	69.1	9.8	72.2	10.9	72.4	13.1
	Treatment	68.9	11.7	71.7	9.1	75.3	11.0
	Change	-0.2	9.0	-0.5	8.8	2.9	10.5

10.1.2.14 Safety Summary

The most common AEs across all treatment groups were abdominal pain (9.6%), constipation (8.5%), and abdominal distension, diarrhea and malaise (7.4% each).

The most common AEs in the placebo group were malaise (13.7%), abdominal pain, abdominal distension, and hypoglycemia (10% each). The most common AEs in the low dose group were

abdominal pain, back pain, and headache (10% each). The most common AEs in the high dose group were constipation and diarrhea (15% each), followed by abdominal pain, vomiting, and gastrointestinal upset (9% each).

There was no meaningful difference in AE profile between treatment groups. There was no meaningful trend in laboratory analyses between groups.

No consistent clinically meaningful laboratory abnormalities are noted. Of note, there was no trend toward increase in uric acid in any of the treatment groups.

There were no meaningful trends in vital signs.

The safety findings in this study closely mirror safety findings in the ISS and safety findings reported in the prior review of this NDA (Fathia Gibril November 2003). The safety findings are similar to, and not readily distinguishable from, findings commonly caused by the underlying disease states.

This study was performed with the CMP.

10.1.2.15 Overall Summary of the New Adult PEI Study (S245.3115)

Efficacy is suggested in the high-dose treatment group of the ITT and the pancreatectomy sub-group of the ITT. However, as described in Section 10.1.2.10 above, since the interim analysis was not pre-specified and the potential effects on measures of statistical success were not provided, no statistical inferences can be made.

This reviewer concludes the efficacy findings of the New Adult PEI can not be used to support efficacy of Creon CMP for treatment of PEI due to PY or CP.

The clinical study was not performed with the CMP and further clinical studies are required with the TbMP.

10.1.3 Descriptions of All Deaths Reported in the Complete Response

10.1.3.1 Deaths Reported in the ISS

Eight deaths were described in the ISS. Seven deaths reported for the first time in this CR. One death was reported in the prior submission of this NDA. These deaths appear attributable to primary disease, known complications of primary disease, and age related secondary pathology (e.g., cardiovascular disease). No deaths appear attributable to treatment with Creon MMS.

Study 223.8.01, patient 111 (Creon MS): The patient was a, 11 ½ year old boy who developed cough, fever, chest pain, respiratory failure and renal failure. This patient had a history of pulmonary complications, methicillin resistant staphylococcus aureus (MRSA), and depression. He entered the study on (b) (6), and was treated with Creon during the run in phase and the treatment phase, commencing on day 9. At an undetermined time during the study, the patient was admitted to the hospital with a four day history of fever, and chest pain, productive cough and shortness of breath. He developed an allergic reaction to an unstated stimulus. He was placed on anti-infective therapy (vancomycin, imipenem, and rifampin) and respiratory therapy (undefined) was initiated. The patient was withdrawn from study on day 20 and parenteral nutrition was initiated, followed by increased oxygen requirement due to respiratory distress. On day 30 the patient died from cardiopulmonary arrest. The events were not felt to be related to the study drug.

The study report for 223.8.01 and the individual case report form for patient 111 are not contained in the NDA update.

Study Creo.630, patient 7 (Creon MS, Creon 12,000): The patient was a 71 year old man with pre-existing history of Parkinsonism and urinary and fecal incontinence who presented with declining appetite and altered general state on study day 58. The patient was hospitalized and diagnosed with a severe dehydration, malnutrition, and a urinary tract infection for which he was started on Bactrim. The patient died on study day 77. The cause of death is not stated. The alteration in mental state was not regarded as related to the study drug. The ISS data set states the cause of AE and subsequent death is not related to study drug. The case report form was reviewed.

Study Creo.630, patient 10 (Creon MS, Creon 12,000): The patient was an 89 year old woman with a history of cardiac insufficiency and atrial fibrillation who died on study day 22 due to acute cardiac decompensation. The AE and death were not related to the study drug. The case report form was reviewed.

Study Creo.630, patient 30 (Creon MS, Creon 12,000): The patient was an 89 year old woman with a previous history of phlebitis and perforated ulcer, who died on study day three due to rupture of a previously undiagnosed aortic aneurysm. The AE and death were not related to the study drug. The case report form was reviewed.

Study Creo.630, patient 5 (Placebo): The patient was an 89 year old woman with a previous history of angina and asthma, who was hospitalized on day 30 due to bronchial infection. She died on day 37 due to cardio-pulmonary decompensation. The AE and death were not related to the study drug. The case report form was reviewed.

Study Creo.630, patient 11 (Placebo): The patient was an 87 year old woman with a previous history of hypertension and "arteriopathy" who died one day after receiving her last placebo dose (day 97). Directly antecedent to death, the patient experienced broncho-pulmonary infection, melena complicated by acute anemia, dehydration, and coma. The AE and death were not felt to be related to administration of placebo. The case report form was reviewed.

Study Creo.631, patient 39 (Placebo): The patient was a 77 year old man with history of carotid and coronary vascular disease who developed cardiovascular failure on treatment day 43 and died on day 44. The AE and death were not felt to be related to administration of placebo. The case report form was reviewed.

Study S245.3.117, patient 1-C-1 (referred to in ISS dataset as patient 1001, Creon MMS): The patient was a 21 year old man with previous history of pulmonary symptoms related to cystic fibrosis. His last dose of study drug was received on day 773, and he was hospitalized for aggravation of cough, which began on day 770. On day 784 he developed respiratory failure. He developed renal failure (day 795) and circulatory failure (day 796). He died on day 802. The Sponsor states the AEs were not treatment emergent and all AEs were unrelated to study drug.

The case report form was reviewed. The day 770 AE, cough, is treatment emergent. A relationship between cough, respiratory failure, and death can not be ruled out. A relationship of the AEs to treatment is unlikely.

10.1.3.2 Deaths Reports Received from Post-Marketing reports or Studies Not Included in the ISS

Ten death reports were received from post-marketing reports or from studies that were not included in the ISS. These deaths appear attributable to primary disease, known complications of primary disease, and age related secondary pathology (e.g., cardiovascular disease). No deaths appear attributable to treatment with Creon MMS.

Study 245.3.103, patient 2102-L-01 (Creon MMS): The patient was a 66 year old woman with a history of pancreatectomy due to carcinoma of the gall bladder. On treatment day 169 hepatic metastasis of gall bladder carcinoma was reported. She discontinued the study due to persistent diarrhea, which the Sponsor attributed to cancer related chemotherapy. Seven months after discontinuation, she died of respiratory failure. The original AE and subsequent death were unrelated to treatment. The case report form was reviewed.

Study S245.3.104, patient 2032-O-04 (Creon MMS): The patient was a 52 year old man with a history of pancreatic carcinoma. He died of liver failure due to metastatic carcinoma. 54 days after completion of the study. Metastasis was diagnosed two days before receipt of first study dose

(placebo in phase 1). The AE and subsequent death were unrelated to treatment. The case report form was reviewed.

Study S245.3.103, patient 2170-L-01 (compassionate use, drug formulation not stated): The patient was a 55 year old male with a history of pancreatic carcinoma who died of recurrent metastatic disease during an open label compassionate use program. The patient was originally enrolled in study S245.3.103 and was treated with Creon in study from December 1996 through April 1999. The patient died in (b) (6). There was no relationship between the AE, subsequent death, and the study medication. No case report form is found for review.

Patient 1030-C-01, (compassionate use, drug formulation not stated): The patient was a 9 year old boy with history of cystic fibrosis who died of respiratory failure during the compassionate use program. Treatment began in November 1996, under Study 245.2.002, and death occurred in (b) (6). No case report form is found for review. The investigator determined the relationship of the AE to treatment and death is temporally related, but casually unrelated. No case report form is found for review.

Patient 2200-C-01 (compassionate use, drug formulation not stated): The patient was a 10 year old girl with cystic fibrosis who died of respiratory failure during the compassionate use program. Treatment began in August 1996, under Study 245.2.002, and was discontinued on 25 October 1998. The patient died on (b) (6). The AE and death occurred were considered unrelated to medication. No case report form is found for review.

Patient 2140-L-02 (compassionate use, drug formulation not stated): The patient was a 70 year old man with a history of chronic pancreatitis, who died of a subdural hemorrhage secondary to a fall, on (b) (6), during the compassionate use program. The patient was originally in Study S245.3.104 and started Creon February 1997 and discontinued treatment on 8 September 1999. The patient died on (b) (6). The AE and death occurred were considered unrelated to medication. No case report form is found for review.

Patient 22 (Protocol Laugier, Creon MS—Burundi): The patient's age is not known. The patient had chronic pancreatitis, cardiomyopathy, and positive HIV serology. During the second month of treatment the patient died; cause unknown. No case report form is found for review.

Patient 21 (Protocol Laugier, Creon MS—Burundi): The patient was 38 years old and had chronic pancreatitis and hypertrophy of the pancreatic head. The patient died of pancreatic cancer during the first month of treatment. No case report form is found for review.

Study S245.4.007, patient 208 (In blinded study not submitted for review; drug formulation not stated): The patient is an 85 year old woman with a history of hypertension and Parkinson's disease, who died of metastatic gastric cancer and pneumonia. She received treatment for suspected pneumonia with penicillin. The AE and subsequent death are not related to treatment. The case report form was reviewed.

Study S245.4.007, patient 403 (In blinded study, study not submitted; drug formulation not stated): The patient was a 75 year old woman who died from recurrent peritoneal carcinosis. The AE and subsequent death are not related to treatment. The case report form was reviewed.

10.1.4 Safety Summary of Three Studies Not Integrated into the ISS

This Reviewer performed brief summary analyses on three of the seven studies which were not integrated into the ISS. This was done to determine if there were notable differences in between the ISS and the non-integrated studies. Because there was sufficient clinical information to make a determination of safety and efficacy based on the bridging study, the two new clinical trials, and the ISS and because the open label nature of these studies limits assessment of causality of AEs, the incidence of common AEs and other safety parameters was not assessed..

The Long Term PEI exposure study was selected because exposure was 48 weeks. The PEI Dose Comparison Study and the 1-Week Adult PEI Study were chosen because patients from these two studies were eligible for enrollment in the Long Term PEI study. Brief descriptions of the studies are presented, followed by presentation of pooled safety data from the three studies.

The Long Term PEI Exposure Study (S245.3.103) was a 48 week, OL, non-PC, dose comparison study of Creon MMS (3 gram/day and 6 gram/day) in 63 patients with PEI due to CP, PY, and other, non-specified, causes of pancreatic insufficiency. The safety population included N=61 patients. The uncontrolled nature of this study precluded substantive review of efficacy; however design allowed for assessment of AEs. On enrollment, patients who were previously enrolled in the PEI Dose Comparison Study and the 1-Week Adult PEI Study, described below, were assigned a unique study-patient identifier. Sixty three patients received Creon MMS, and no patients received placebo.

The PEI Dose Comparison Study (K245.5.703) was three week OL study of Creon MMS in 43 adults with PEI due to CP or PY. All patients received 5-days of OL placebo treatment. After completion of the placebo phase, 41 patients were randomized into one of two active treatment sub-studies. In one sub-study, patients were treated with either of two fixed doses (3 gram/day or 6 gram/day) for 1-2 weeks. In the other sub-study patients were treated with a progressive dose regimen—in sequence: 0.75 gram/day for one week, 1.5 gram/day for one week, and 3 gram/day for one week. On completion, patients were eligible for enrollment in S245.3.103. The uncontrolled nature of this study precluded substantive review of efficacy; however design allowed for assessment of AEs. Forty three patients received placebo, and 41 patients received Creon MMS.

The 1-Week Adult PEI Study (S245.3.104) was a 4 week OL study of Creon MMS in 85 adults with PEI due to CP or PY, and other, non-specified, causes of pancreatic insufficiency. After a 5-day, open-label placebo treatment period, patients received 4 weeks of open-label treatment with Creon MMS. The uncontrolled nature of this study precluded substantive review of efficacy; however design allowed for assessment of AEs. Eight-five patients received placebo and 83 patients received Creon MMS. On completion, patients were eligible for enrollment in S245.3.103.

There were 162 individual patients in the safety set from the above studies. No SAE was counted more than once due to enrollment in more than one of the three studies. Patients who enrolled in the Long Term PEI Exposure study after enrollment in either of the two other studies were assigned new unique patient identifiers. The final number of unique patient identifiers (hereafter, patients) is 187. One hundred eighty seven patients received Creon MMS and 128 patients received placebo.

SAEs were reported in 11% of the 187 patients. The most common SAEs by SOC were gastrointestinal disorders, infections and infestations, and neoplasm. The most common SAEs b PT were vomiting (1.6% of patients), and nausea, liver abscess, liver metastasis, and recurrent pancreatic carcinoma (each reported in 1% of patients). Of note, there were no treatment emergent SAEs (TE-SAEs) in the PEI Dose Comparison Study. These findings are summarized in 54 below.

Table 54: SAEs in Patients Receiving MMS In Three Non-integrated Studies

All patients in safety set who received MMS, N=187		Events	N	%
		31	20	11
SOC	Preferred Term			
Cardiac disorders	Pulmonary edema NOS	1	1	0.5
Gastrointestinal disorders	Vomiting NOS	3	3	1.6
	Nausea	2	2	1
	Pancreatitis acute on chronic	2	1	0.5
	Abdominal pain upper	1	1	0.5
	Diarrhea NOS	1	1	0.5
	Ileus paralytic	1	1	0.5
General disorders and administration site conditions	Malaise	1	1	0.5
	Pyrexia	1	1	0.5
Hepatobiliary disorders	Hepatic function abnormal NOS	1	1	0.5
Infections and infestations	Liver abscess	2	2	1
	Enterocolitis infectious	1	1	0.5
	Influenza	1	1	0.5
	Sepsis NOS	1	1	0.5
Injury, poisoning and procedural complications	Brain contusion	1	1	0.5
	Fractured pelvis NOS	1	1	0.5
Metabolism and nutrition disorders	Malnutrition NOS	2	1	0.5
Musculoskeletal and connective tissue disorders	Back pain aggravated	1	1	0.5
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Metastases to liver	2	2	1
	Pancreatic carcinoma recurrent	2	2	1
	Metastases to lung	1	1	0.5
Renal and urinary disorders	Hematuria	1	1	0.5
Respiratory, thoracic and mediastinal disorders	Epistaxis	1	1	0.5

Except for one patient with hypoglycemia not otherwise specified, there were no SAEs in the placebo treated group,; therefore, the placebo column is not shown.

The frequency of SAEs in the non-integrated long term studies was 11% for any SAE and between 0.5 and 1.6% for SAEs classified by PT. The most common SAEs in the long-term studies were vomiting (1.6%), nausea (1%), and pancreatitis (1%); primary, recurrent, or metastatic carcinoma (0.5 to 1%); infections and infestations (0.5 to 1%); and liver abscess (1%). The carcinoma SAEs all reflect entry diagnoses.

This reviewer concluded the SAEs reported in these three studies reflect pre-existing enrollment diagnoses, and do not differ substantially to SAEs reported in the ISS. The relatively common finding of carcinoma is related to baseline diagnoses and is not thought by this reviewer to be related to medication effects

10.1.5 Additional Tables

Table 55: All Dropouts listed in ISS, by Drug or Placebo Treatment

All Patients who dropped out by treatment group		All Patients (N=1,546)		MMS (N=594)		MS (N=991)		Placebo (N=589)	
		N	%	N	%	N	%	N	%
		53	3.4	14	2.4	19	1.9	17	2.9
Listing of Individual AEs									
SOC	Preferred Term	N	%	N	%	N	%	N	%
Blood and lymphatic system disorders	Iron deficiency anemia	1	0.1	0	0	0	0	1	0.2
Cardiac disorders	Cardiac failure	2	0.1	0	0	1	0.1	1	0.2
	Acute myocardial infarction	1	0.1	0	0	0	0	1	0.2
	Cardiovascular disorder	1	0.1	0	0	0	0	1	0.2
Ear and labyrinth disorders	Ear pain	1	0.1	0	0	0	0	1	0.2
	Vertigo	1	0.1	0	0	0	0	1	0.2
Endocrine disorders	Hyperthyroidism	1	0.1	0	0	0	0	1	0.2
Gastrointestinal disorders	Abdominal pain	10	0.7	6	1.0	3	0.3	1	0.2
	Diarrhea	7	0.5	4	0.7	2	0.2	1	0.2
	Nausea	7	0.5	3	0.5	4	0.4	0	0
	Vomiting	7	0.5	2	0.3	4	0.4	1	0.2
	Abdominal pain upper	3	0.2	0	0.0	2	0.2	1	0.2
	Constipation	2	0.1	1	0.2	1	0.1	0	0
	Flatulence	2	0.1	2	0.3	0	0.0	0	0
	Abdominal discomfort	1	0.1	1	0	0	0.0	0	0
	Abdominal distension	1	0.1	1	0	0	0.0	0	0
	Distal intestinal obstruction syndrome	1	0.1	1	0	0	0.0	0	0
	Frequent bowel movements	1	0.1	1	0	0	0.0	0	0
	Pancreatic pseudocyst	1	0.1	0	0	1	0.1	0	0
	Pancreatitis	1	0.1	0	0	0	0.0	1	0.2
	Pancreatitis acute	1	0.1	0	0	0	0.0	1	0.2
	Pancreatitis chronic	1	0.1	0	0	1	0.1	0	0
	Rectal hemorrhage	1	0.1	0	0	1	0.1	0	0
General disorders and administration site conditions	Drug withdrawal syndrome	1	0.1	0	0	1	0.1	0	0
	General symptom	1	0.1	0	0	0	0	1	0
	Heparin-induced thrombocytopenia	1	0.1	0	0	0	0	1	0
	Influenza like illness	1	0.1	0	0	1	0.1	0	0
	Pain	1	0.1	0	0	1	0.1	0	0
Infections and infestations	Superinfection lung	2	0.1	0	0	0	0	2	0.3
	Appendiceal abscess	1	0.1	1	0	0	0.0	0	0
	Respiratory tract infection	1	0.1	0	0	1	0.1	0	0
	Sinusitis	1	0.1	0	0	0	0	1	0.2
	Urinary tract infection	1	0.1	0	0	1	0	0	0.0
Investigations	Blood thyroid stimulating hormone decreased	1	0.1	0	0	0	0	1	0.2

Table 55: All Dropouts listed in ISS, by Drug or Placebo Treatment

All Patients who dropped out by treatment group		All Patients (N=1,546)		MMS (N=594)		MS (N=991)		Placebo (N=589)	
		N	%	N	%	N	%	N	%
		53	3.4	14	2.4	19	1.9	17	2.9
Listing of Individual AEs									
SOC	Preferred Term	N	%	N	%	N	%	N	%
Metabolism and nutrition disorders	Dehydration	3	0.2	0	0	3	0.3	0	0
	Hypoglycemia	2	0.1	0	0	1	0.1	1	0.2
	Hyperglycemia	1	0.1	0	0	1	0.1	0	0
	Ketoacidosis	1	0.1	0	0	1	0.1	0	0
	Malnutrition	1	0.1	0	0	1	0.1	0	0
Musculoskeletal and connective tissue disorders	Muscle spasms	2	0.1	2	0.3	0	0	0	0
Nervous system disorders	Dizziness	1	0.1	1	0.2	0	0	0	0
	Headache	1	0.1	0	0	0	0	1	0.2
	Syncope	1	0.1	0	0	0	0	1	0.2
	Tremor	1	0.1	1	0.2	0	0	0	0
Psychiatric disorders	Abnormal behavior	1	0.1	0	0	0	0	1	0.2
Renal and urinary disorders	Renal failure	1	0.1	1	0.2	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Cough	2	0.1	2	0.3	0	0	0	0
	Increased bronchial secretion	1	0.1	1	0.2	0	0	0	0
	Respiratory failure	2	0.1	1	0.2	0	0	1	0.2
	Acute respiratory failure	1	0.1	0	0	0	0	1	0.2
	Dyspnea	1	0.1	1	0.2	0	0	0	0
	Hyperventilation	1	0.1	1	0.2	0	0	0	0
	Productive cough	1	0.1	1	0.2	0	0	0	0
	Pulmonary edema	1	0.1	0	0	0	0	1	0.2
Surgical and medical procedures	Surgery	1	0.1	0	0	1	0.1	0	0
Vascular disorders	Aneurysm ruptured	1	0.1	0	0	1	0.1	0	0
	Shock	1	0.1	1	0.2	0	0	0	0

Table 56: All SAEs reported in the ISS

SAEs Occurring any Patient Reported in the ISS		Total (N=1,546)		MMS (N=594)		MS (N=991)		Other PEP[1] (N=311)		Placebo (N=589)	
		N	%	N	%	N	%	N	%	N	%
		95	6.1	20	3.4	48	4.8	5	1.3	21	3.4
SOC	**Preferred Term**	**Listing of Individual SAEs**									
Blood and lymphatic system disorders	Anemia	1	0.1	1	0.2	0	0	0	0	0	0
Cardiac disorders	Cardiac failure	2	0.1	0	0	1	0.1	0	0	1	0.2
	Acute myocardial infarction	1	0.1	0	0	0	0	0	0	1	0.2
	Atrial tachycardia	1	0.1	1	0.2	0	0	0	0	0	0
	Cardiovascular disorder	1	0.1	0	0	0	0	0	0	1	0.2
	Right ventricular failure	1	0.1	1	0.2	0	0	0	0	0	0
Gastrointestinal disorders	Abdominal pain	7	0.5	1	0.2	5	0.5	0	0	1	0.2
	Vomiting	4	0.3	1	0.2	3	0.3	0	0	0	0
	Nausea	3	0.2	0	0	3	0.3	0	0	0	0
	Pancreatitis acute	2	0.1	0	0	0	0	0	0	2	0.3
	Pancreatitis chronic	2	0.1	0	0	2	0.2	0	0	0	0
	Abdominal pain upper	1	0.1	0	0	1	0.1	0	0	0	0
	Acute abdomen	1	0.1	1	0.2	0	0	0	0	0	0
	Diarrhea	1	0.1	1	0.2	0	0	0	0	0	0
	Distal intestinal obstruction syndrome	1	0.1	1	0.2	0	0	0	0	0	0
	Gastrointestinal disorder	1	0.1	1	0.2	0	0	0	0	0	0
	Gastroesophageal reflux disease	1	0.1	1	0.2	0	0	0	0	0	0
	Impaired gastric emptying	1	0.1	1	0.2	0	0	0	0	0	0
	Intestinal obstruction	1	0.1	0	0	0	0	1	0.3	0	0
	Intussusception	1	0.1	1	0.2	0	0	0	0	0	0
	Meconium ileus	1	0.1	1	0.2	0	0	0	0	0	0
	Melena	1	0.1	0	0	0	0	0	0	1	0.2
	Pancreatic pseudocyst	1	0.1	0	0	1	0.1	0	0	0	0
	Pancreatitis	1	0.1	0	0	0	0	0	0	1	0.2
	Stomatitis	1	0.1	1	0.2	0	0	0	0	0	0
General disorders and administration site conditions	Pyrexia	7	0.5	4	0.7	2	0.2	0	0	1	0.2
	Pain	2	0.1	0	0	1	0.1	1	0.3	0	0
	Cyst	1	0.1	0	0	1	0.1	0	0	0	0
	Drug withdrawal syndrome	1	0.1	0	0	1	0.1	0	0	0	0
	Heparin-induced thrombocytopenia	1	0.1	0	0	0	0	0	0	1	0.2
	Edema	1	0.1	0	0	0	0	0	0	1	0.2
Infections and infestations	Bronchitis acute	3	0.2	2	0.3	1	0.1	0	0	0	0
	Pneumonia[1]	8	0.5	1	0.2	6	0.6	0	0	0	0
	Superinfection lung	3	0.2	0	0	0	0	0	0	3	0.5
	Influenza	2	0.1	1	0.2	0	0	1	0.3	0	0
	Lower respiratory tract infection	2	0.1	2	0.3	0	0	0	0	0	0
	Urinary tract infection	2	0.1	0	0	2	0.2	0	0	0	0
	Acute tonsillitis	1	0.1	0	0	1	0.1	0	0	0	0

Table 56: All SAEs reported in the ISS

SAEs Occurring any Patient Reported in the ISS		Total (N=1,546)		MMS (N=594)		MS (N=991)		Other PEP[1] (N=311)		Placebo (N=589)	
		N	%	N	%	N	%	N	%	N	%
		95	6.1	20	3.4	48	4.8	5	1.3	21	3.4
SOC	**Preferred Term**	**Listing of Individual SAEs**									
	Appendiceal abscess	1	0.1	1	0.2	0	0	0	0	0	0
	Herpes virus infection	1	0.1	1	0.2	0	0	0	0	0	0
	Infection	1	0.1	0	0	1	0.1	0	0	0	0
	Lung infection pseudomonal	1	0.1	1	0.2	0	0	0	0	0	0
	Nasopharyngitis	1	0.1	0	0	1	0.1	0	0	0	0
	Pseudomonas infection	1	0.1	0	0	1	0.1	0	0	0	0
	Respiratory tract infection	1	0.1	0	0	1	0.1	0	0	0	0
	Sepsis	1	0.1	0	0	0	0	0	0	1	0.2
	Sinusitis	1	0.1	0	0	1	0.1	0	0	0	0
Injury, poisoning and procedural complications	Femoral neck fracture	1	0.1	0	0	1	0.1	0	0	0	0
	Injury	1	0.1	0	0	0	0	0	0	1	0.2
	Near drowning	1	0.1	0	0	1	0.1	0	0	0	0
	Subdural hematoma	1	0.1	0	0	0	0	0	0	1	0.2
Metabolism and nutrition disorders	Hypoglycemia	5	0.3	0	0	2	0.2	0	0	3	0.5
	Dehydration	3	0.2	0	0	3	0.3	0	0	0	0
	Hyperglycemia	1	0.1	0	0	1	0.1	0	0	0	0
	Ketoacidosis	1	0.1	0	0	1	0.1	0	0	0	0
	Malnutrition	1	0.1	0	0	1	0.1	0	0	0	0
Musculoskeletal and connective tissue disorders	Back pain	2	0.1	1	0.2	0	0	0	0	1	0.2
	Neck pain	1	0.1	0	0	0	0	0	0	1	0.2
Nervous system disorders	Dizziness	1	0.1	0	0	0	0	0	0	1	0.2
	Hypoglycemic coma	1	0.1	0	0	0	0	0	0	1	0.2
	Metabolic encephalopathy	1	0.1	1	0.2	0	0	0	0	0	0
	Migraine	1	0.1	0	0	0	0	0	0	1	0.2
	Syncope	1	0.1	0	0	0	0	0	0	1	0.2
Psychiatric disorders	Anxiety	1	0.1	0	0	1	0.1	0	0	0	0
	Depression	1	0.1	0	0	1	0.1	0	0	0	0
	Suicide attempt	1	0.1	0	0	0	0	1	0.3	0	0
Renal and urinary disorders	Renal failure	1	0.1	1	0.2	0	0	0	0	0	0
	Renal impairment	1	0.1	1	0.2	0	0	0	0	0	0
Reproductive system and breast disorders	Testicular torsion	1	0.1	1	0.2	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Cough	3	0.2	3	0.5	0	0	0	0	0	0
	Lung disorder	8	0.5	1	0.2	7	0.7	0	0	0	0
	Bronchial obstruction	2	0.1	2	0.3	0	0	0	0	0	0
	Hemoptysis	2	0.1	1	0.2	1	0.1	0	0	0	0
	Productive cough	2	0.1	2	0.3	0	0	0	0	0	0
	Respiratory failure	2	0.1	1	0.2	0	0	0	0	1	0.2
	Acute respiratory failure	1	0.1	0	0	0	0	0	0	1	0.2
	Bronchospasm	1	0.1	0	0	1	0.1	0	0	0	0
	Dyspnea	1	0.1	1	0.2	0	0	0	0	0	0
	Pharyngolaryngeal pain	1	0.1	1	0.2	0	0	0	0	0	0

Table 56: All SAEs reported in the ISS

SAEs Occurring any Patient Reported in the ISS		Total (N=1,546)		MMS (N=594)		MS (N=991)		Other PEP[1] (N=311)		Placebo (N=589)	
		N	%	N	%	N	%	N	%	N	%
		95	6.1	20	3.4	48	4.8	5	1.3	21	3.4
SOC	**Preferred Term**	**Listing of Individual SAEs**									
	Pulmonary edema	1	0.1	0	0	0	0	0	0	1	0.2
	Respiratory disorder	1	0.1	0	0	1	0.1	0	0	0	0
	Tachypnea	1	0.1	1	0.2	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	Cold sweat	1	0.1	0	0	0	0	0	0	1	0.2
Surgical and medical procedures	Surgery	2	0.1	0	0	2	0.2	0	0	0	0
	Gastrostomy tube insertion	1	0.1	1	0.2	0	0	0	0	0	0
	Hospitalization	1	0.1	0	0	0	0	1	0.3	0	0
	Limb operation	1	0.1	0	0	1	0.1	0	0	0	0
	Respiratory therapy	1	0.1	0	0	1	0.1	0	0	0	0
Vascular disorders	Aneurysm ruptured	1	0.1	0	0	1	0.1	0	0	0	0
	Shock	1	0.1	1	0.2	0	0	0	0	0	0

[1]One of eight patients with SAE categorized as pneumonia was in the post-treatment period > 14 days after last dose of drug or placebo.
[2] Table does not include six non-treatment emergent SAEs which occurred in 3 patients during the pre-treatment period. These SAEs included three upper respiratory tract infections in one person reported on the same day; one cough in one person; one episode of acute otitis media in one person; and one episode of salmonella gastroenteritis.
[3] Including Cotazym, Pancrease, Pancrex, and Panzytrat commercial PEPs

Table 57: AEs in ≥ 1% of Patients Where Seriousness was listed as Unknown

All AEs; Unknown Seriousness		Total (N=406)		MS (N=276)		Other PEPs (N=125)		Placebo (N=131)	
		N	%	N	%	N	%	N	%
		187	46	143	52	74	59	21	16
AEs in ≥ 1% of patients									
SOC	Preferred Term								
Gastrointestinal	Abdominal pain	58	14	32	12	25	23	1	1
	Diarrhea	38	9	23	8	13	18	2	2
	Vomiting	35	9	19	7	13	16	3	2
	Abnormal feces	26	6	13	5	13	21	0	0
	Nausea	20	5	11	4	5	6	4	3
	Abdominal distension	10	3	5	2	5	4	0	0
	Abdominal pain upper	11	3	5	2	6	6	0	0
	Constipation	8	2	3	1	5	6	0	0
	Flatulence	4	1	2	1	2	2	0	0
	Hematochezia*	3	1	3	1	0	0	0	0
General and administration site	Pyrexia	17	4	12	4	5	4	0	0
	Pain	12	3	8	3	2	2	2	2
	Malaise	10	3	6	2	4	4	0	0
Infections and infestations	Nasopharyngitis	17	4	14	5	3	2	0	0
	Rhinitis	16	4	12	4	4	5	0	0
Metabolism and nutrition	Anorexia	12	3	6	2	6	5	0	0
Nervous system	Headache	26	6	15	5	7	13	2	2
Respiratory, thoracic and mediastinal	Cough	47	12	35	13	12	11	0	0
	Lung disorder	17	4	10	4	7	6	0	0
	Productive cough	11	3	9	3	2	2	0	0

[1]AE=Non serious AEs and AEs of unknown seriousness
[2] N=Number of persons experiencing events.
[3] Population: Total patients in (1) studies where seriousness assessment was not planned and (2) studies wherein seriousness was not assigned to at least one AE.
* AE > 1% in subgroup.

Table 58: Multiple Dose studies, electronically reproduced from Sponsor's table 8.8.1; Vol. 26, p 9485-7

Study	N			Blind	Design	Duration of Tx	Drug (Duration)	Control/Other Drug	Remarks
	1	2	3						
Cystic Fibrosis with PEI									
223.8.01	33	-	33 (32)	Open	2-CO	5 weeks	MS 25000 (2 wks)	MS 8000 (2 wks)	1 week run-in with MS 8000
K.224.5001	89	-	89	DB	2-CO	8 weeks	MS 25000 (4 wks)	Panzytrat 20000 (4 wks)	
K.224.5006	46	-	45	Open	S	26 weeks	MS 25000 (13 wks)	Pancrease 5000, MS 8000 (13 wks)	Pancrease 5000 or MS 8000 during Phase 1 and MS 25000 during Phase 2
K.224.5010	18	-	14	Open	2-CO	6-10 weeks	MS 25000 (2 wks)	Cotazym Forte (2 wks)	2-6 weeks run-in with Cotazym Forte
K.245.5002	69	69	69	Open	2-CO	4 weeks	MMS 10000 (2 wks)	MS 12000 (2 wks)	
K.245.5004	34	33	34 (33)	DB	2-CO	7 weeks	MMS 10000 (2 wks)	MS 8000 (2 wks)	3 weeks run-in with MS 8000
KREON.586	27	-	27	DB	2-CO	10 weeks	MS 8000 (4 wks)	Pancrease 5000 (4 wks)	2 weeks run-in with MS 8000
KREON 84/02	20	-	20	DB	2-CO	8 weeks	MS 8000 (4 wks)	Pancrex V Forte 5600 (4 wks)	
KREON 84/03	21	-	21	Open	2-CO	8 weeks	MS 8000 (4 wks)	Pancrex V Forte 5600 (4 wks)	
KREO.584	29	-	29	Open	S	104 weeks	MS 8000 (104 wks)	-	
KREO.592	17	-	17	Open	2-CO	12 weeks	MS 8000 (6 wks)	MS 8000 (6 wks)	capsules versus sachets
KREO.629 *	11	11	-	SB	S	12 days	MMS 10000 (6 days)	Placebo (6 days)	
KREO.636	64	-	63	Open	2-CO	2 weeks	MS 8000 (1 wk)	Pancrease (1 wk)	
RR.1044-01	21	-	21	Open	2-CO	4 weeks	MS 8000 (2 wks)	Pancrease (2 wks)	
S223.3.101	47	47 (18)	-	DB	2-PG	2-3 weeks	MMS 20000 (1 wk)	Placebo (1 wk)	1-2 weeks run-in with MMS 20000
S223.3.102	50	50 (18)	-	DB	2-PG	2-3 weeks	MMS 20000 (6 days)	Placebo (6 days)	1-2 weeks run-in with MMS 20000
S245.3.105	59	57	59 (55)	Open	2-CO	10 weeks	MMS 10000 (4 wks)	MS 8000 (4 wks)	2 weeks run-in with MS 8000
S245.3.117 *	3	3	-	Open	S	not fixed	MMS 10000	-	The sachets administered contained 20000 lipase units of Creon MMS 10000. Max trtmt duration before cut-off: > 4 yrs
S245.3.118 *	40	40	-	Open	2-CO	30 days	Creon for children	MMS 12000 (15 days)	

Table 58: Multiple Dose studies, electronically reproduced from Sponsor's table 8.8.1; Vol. 26, p 9485-7

Study	N			Blind	Design	Duration of Tx	Drug (Duration)	Control/Other Drug	Remarks
	1	2	3						
							(MMS) (15 days)		
S248.3.002	33	29	33 (29)	DB	2-CO	7 weeks	MMS 25000 (2 wks)	MS 25000 (2 wks)	3 weeks run-in with MS 25000
S248.3.003 *	12	12	-	Open	S	8 weeks	Creon for children (MMS) (8 wks)	-	
Chronic Pancreatitis with PEI									
223.2.01	27	13	-	DB	2-PG	4 weeks	MMS 10000 (2 wks)	Placebo (2 wks)	2 wks run-in with placebo
CREO.635 *	20	-	19	DB	2-CO	4 weeks	MS 8000 (2 wks)	Placebo (2 wks)	
K.224.5003	11	-	11	DB	2-CO	5 weeks	MS 25000 (2 wks)	Pancrease 6200 (2 wks)	1 wk run-in with Pancrease
K.224.5008	6	-	6	Open	S	3 weeks	MS 25000 (2 wks)	-	1 wk run-in with placebo
K.224.5009	24	-	24	DB	2-CO	20 days	MS 25000 (10 days)	Pancrease (10 days)	
K.224.5016	65	-	64	DB	2-CO	5 weeks	MS 25000 (2 wks)	MS 8000 (2 wks)	1 wk run-in with placebo
K.245.5003	37	23	28 (23)	DB	2-CO	7 weeks	MMS 10000 (2 wks)	MS 10000 (3 wks)	1 wk run-in with placebo and 1 wk with MS 10000
K.245.5005	40	17	39	DB	2-PG	4 weeks	MMS 10000 (2 wks)	Placebo (2 wks)	1 wk run-in with placebo and 1 wk with MS 10000
KREO.628	31	-	30	DB	3-CO	12 weeks	MS 10000 (8 wks)	Placebo (4 wks)	
RR.1044-03	58	-	57	DB	2-CO	8 weeks	MS 8000 (4 wks)	Placebo (4 wks)	
S245.3.107 *	3	4	-	DB	2-CO	4 weeks	MMS 10000 (1 wk)	Placebo (1 wk)	1w run-in with placebo and 1 wk with MMS 10000
S245.3.115-CP*	35	23		DB	3-PG	7 days	MMS 10000 (1 wk) (two dose groups)	Placebo (1 wk)	The sachets contained 20000 lipase units of Creon MMS 10000. The study included patients with CP and patients with PY. Only patients with CP are counted here
Pancreatectomy with PEI									
K.224.5002	40	-	40 (39)	DB	2-CO	6 wks	MS 25000 (2 wks)	MS 8000 (2 wks)	2 wks run-in with MS 8000, Pancreatectomy
RK.223.00.02	16	-	16 (7)	DB	2-PG	8 wks	MS 8000 (4 wks)	Placebo (4 wks)	4 wks run-in with MS 8000, Pancreatectomy
S248.3.001	27	21	27	DB	2-CO	6 wks	MMS 25000	MS 8000 (2	2 wks run-in with MS

Table 58: Multiple Dose studies, electronically reproduced from Sponsor's table 8.8.1; Vol. 26, p 9485-7

Study	N			Blind	Design	Duration of Tx	Drug (Duration)	Control/Other Drug	Remarks
	1	2	3						
			(21)				(2 wks)	wks)	8000, Pancreatectomy
S245.3.102	11	3	9	DB	2-PG	4 wks	MMS 20000 (2 wks)	Placebo (2 wks)	1 wk run-in with placebo and 1 wk with MS 10000, Gastrectomy
S245.3.115-PY*	59	41	-	DB	3-PG	7 days	MMS 10000 (1 wk) (two dose groups)	Placebo (1 wk)	1w run-in with placebo. The sachets contained 20000 lipase units of Creon MMS 10000. The study included patients with CP and patients with PY. Only patients with PY are counted here.
Acute Pancreatitis with PEI									
S248.4.001 *	56	27	-	DB	2-PG	26-30 days	MMS 25000 (26-30 days)	Placebo (26-30 days)	
S248.4.002 *	21	10	-	DB	2-PG	84 days	MMS 25000 (84 days)	Placebo (84 days)	
Diabetes Mellitus with PEI									
S245.3.112	6	3	-	DB	2-PG	7 days	MMS 10000 (7 days)	Placebo (7 days)	
S245.3.113	23	13	-	DB	2-PG	7 days	MMS 10000 (7 days)	Placebo (7 days)	
Diabetes Mellitus without PEI									
S245.3.110	80	39	-	DB	2-PG	16 wks	MMS 10000 (16 wks)	Placebo (16 wks)	
HIV without PEI									
S245.3.116*	10	6	-	DB	2-PG	4 wks	MMS 10000 (4 wks)	Placebo (4 wks)	
Chronic Malnutrition in the Elderly without PEI									
CREO.630 *	52	-	26	DB	2-PG	90 days	MS 12000 (90 days)	Placebo (90 days)	
CREO.631 *	44	-	21	DB	2-PG	90 days	MS 12000 (90 days)	Placebo (90 days)	

* Newly integrated since NDA Update 2002
Blind: DB=double-blind SB=single-blind Open=open-label Test/control drug: MS = Creon microspheres, MMS = Creon minimicrospheres
Design: PG=parallel groups CO=cross-over (the preceding number is the number of treatments) S=single treatment/sequential design
N: (1) = number of patients randomized
(2) = number of patients who took Creon MMS (first number includes run-in, second number not)
(3) = number of patients who took Creon MS (first number includes run-in, second number not)

Table 59, Single Dose studies, electronically reproduced from Sponsor's table 8.8.1; Vol. 26, p 9489

Indication	N			Blind	Design	Duration of Treatment	Test Drug (Duration)	Control/Other Drug
	1	2	3					
Cystic Fibrosis with PEI								
S245.3.111	21	20	-	Open	3-CO	single dose	MMS 10000	Pancrease, Placebo
S245.4.004^	12	12	-	DB	3-CO, 4 trtmt	single dose	MMS 5000, 15000, 40000	Placebo
S248.2.001^	11	11		Open	S	single dose	MMS 25000	-
Chronic Pancreatitis with PEI								
K.224.5011^	5	5	-	DB	2-CO	single dose	MMS 25000	Placebo
S245.2.003	14	14	-	DB	2-CO	single dose	MMS 12000	MMS 10000

^ Study report presented to FDA in 2002
Blind: DB=double-blind SB=single-blind Open=open-label Test/control drug: MS = Creon microspheres, MMS = Creon minimicrospheres
Design: PG=parallel groups CO=cross-over (The preceding number is the number of CO periods. The number of treatments (trtmt) is given if different from the number of CO periods)
S=single treatment/sequential design
N: (1) = number of patients randomized
(2) = number of patients who took Creon MMS
(3) = number of patients who took Creon MS

Table 59: Table of studies not integrated due to data integrity issues; electronically copied from the Sponsor's submission (Volume 26, page 9490)

		N						
Study Code	1	2	3	Blind	Design	Duration of Treatment	Test Drug (Duration)	Control/Other Drug
K.245.5703	26 (17)	24 (17)	--	Open	2-PG S	1-2 weeks 3 weeks	MMS 10000 (1-2 wks) (two dose groups) MMS 10000 (3 wks) (three doses sequentially, 1 wk for each)	5 days run-in with placebo were followed by a period with two parallel dose groups, which was then followed by a period during which three doses were given sequentially. The numbers in the second line refer to the latter period. The study included both patients with CP and patients with pancreatectomy.
S245.3.103	63	63	--	Open	S	24-52 weeks	MMS 10000 (24-52 wk)	Partly extended from S245.3.104. The study included patients with CP, patients with pancreatectomy, and patients with gastrectomy.
S245.3.104	85	83	-	Open	S	4 weeks	MMS 10000 (4 wk)	5 days run-in with placebo.
								The study included patients with CP, patients with pancreatectomy, and patients with gastrectomy.
S245.2.002	5	5	-	Open	S	53 weeks	MMS 10000 (53 wk)	5 days run-in with placebo
								The study included patients with CF.
S245.4.007	45	unk (4)	unk (4)	DB	2-PG	6 months	MMS 25000 (6 months)	Placebo (6 months), still blinded. Patients with gastrectomy.
S245.3.119	38	38	-	DB	2-CO	4 wks	MMS 25000 (2 wks)	Placebo (2 wks), not reported by cut-off date. HIV patients.
Laugier	26	26	-	DB	2-PG	6 months	MS 12000	No full study report available. Patients with chronic pancreatitis.

Blind: DB=double-blind SB=single-blind Open=open-label Test/control drug: MS = Creon microspheres, MMS = Creon minimicrospheres
Design: PG=parallel groups CO=cross-over (The preceding number is the number of CO periods. The number of treatments (trtmt) is additionally given if different from the number of CO periods)
S=single treatment/sequential design
N: (1) = number of patients randomized, (2) = number of patients who took Creon MMS, (3) = number of patients who took Creon MS,
(4) unknown because the study was still blinded

10.2 References

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2 Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol. 2006;20(3):531-46. (PMID: 1470282)

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4 Sack J, Blau H, Goldfarb D, Ben-Zaray S, Katznelson D. Hyperuricosuria in cystic fibrosis patients treated with pancreatic enzyme supplements. A study of 16 patients in Israel. Isr J Med Sci. 1980 Jun;16(6):417-9. (PMID: 6901713)

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/s/

Ethan Hausman
8/16/2007 01:52:35 PM
MEDICAL OFFICER

Anne Pariser
8/16/2007 02:02:06 PM
MEDICAL OFFICER

Clinical Team Leader Summary Review of NDA 20-725
Creon® (pancrelipase delayed-release capsules) for Exocrine Pancreatic Insufficiency

Date: July 31, 2007

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

To: Daniel A. Shames, M.D., Deputy Director, Office of Drug Evaluation 3 (ODE 3)
Julie G. Beitz, M.D., Director, ODE 3

Identifying Information

NDA #:	20-725
Applicant:	Solvay Pharmaceuticals
Product name:	pancrelipase delayed-release capsules
Proposed Trade Name:	Creon®
Submission date:	November 17, 2006
Stamp date:	November 20, 2006
PDUFA goal date:	August 17, 2007
Formulation:	Creon® 6, 12, and 24 capsules for oral administration
Proposed indication:	Treatment of steatorrhea due to exocrine pancreatic insufficiency (EPI)
Proposed regimen:	1,000 to 3,000 lipase units per kg per meal, not to exceed 10,000 lipase units per kg per day

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

I. Introduction, Background, and Regulatory History

A. Introduction

This submission is a Complete Response (CR) to the Not Approvable (NA) action taken for the Creon® New Drug Application (NDA) in November 2003. Creon is a New Molecular Entity (NME). This CR submission was received on 20-November-2006, there was a major amendment to the submission on 24-April-2007, and the Prescription Drug User Fee Act (PDUFA) goal date is 17-August-2007.

B. Clinical Background

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

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

C. Regulatory History of Pancreatic Enzyme Products

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

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

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

- In 1979, the Agency proposed establishing monographs for OTC PEPs.

- In 1985, recommendations of the PEP Advisory Review Panel were published that stated that OTC monographs would not be sufficient to regulate the PEPs, preclearance of each product to standardize enzyme bioactivity would be necessary, and PEPs should be made available by prescription only.

- In 1991, the Expert panel proposed that the FDA withdraw the 1985 proposed OTC rule, declared that the PEPs are not Generally Recognized as Safe (GRAS) and Generally Recognized as Effective (GRAE), and the PEPs are misbranded.

- In 1995, a Notice of Final Rule was published that stated all PEPs must obtain FDA approval (under NDA) in order to remain on the market.

- In 2004, the Notice of Requirement for NDA Approval was published that stated all PEPs must get NDA approval within the next four years (deadline 28-April-2008), and the expectation of the Agency was that only NDAs under 505(b)(2), not Abbreviated New Drug Applications (ANDAs), would be received. To be approved, PEP NDAs must meet the requirements for content and format of an

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

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

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

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

D. Regulatory History of Creon®

The regulatory history for Creon is summarized as follows:

- The original NDA submission for Creon was on 31-July-1991 (received 01-August-1997). The Application was placed under Application Integrity Policy (AIP) on 24-September-1997 for data integrity issues, and review of the NDA was suspended. The AIP status was revoked on 09-April-2003, and review of the NDA resumed as a priority review.

- On 09-October-2003, Solvay (the Applicant) was issued a Not Approvable (NA) letter for the Creon NDA by the Division. Major deficiencies noted were predominantly Chemistry, Manufacturing and Controls (CMC) deficiencies, including:
  - The drug master file (DMF) for drug substance (DS) was inadequate to support the NDA.
  - Adequate acceptance specifications, including specific tests for identity, purity, and potency were to be provided.
  - Reference standards for DS and drug product (DP) needed to be developed.
  - Robust viral clearance during DS manufacturing needed to be demonstrated.
  - Adequate consistency and stability of the DS needed to be demonstrated.
  - Adequate specifications for the DP needed to be established. The use of (b) (4)
  - Adequate consistency and stability of the DP, based on adequate specifications and an acceptable stability protocol needed to be demonstrated.

[1] U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). "Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs." 2004.

[2] U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). "Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs." <http://www.fda.gov/cder/guidance/6275fnl.htm> April 2006.

- In addition to the major CMC deficiencies noted (above), the Division communicated to the Applicant that once the chemistry deficiencies were corrected, the Applicant would need to link the intended to-be-marketed formulation with the formulation used in the clinical trials. The Division also stated that data to support the use of Creon in children under the age of seven would need to be provided. In additional discussions held between the Applicant and Division after issuance of the NA letter, the Applicant stated their intent to link the formulation used in clinical trials with the intended to-be-marketed formulation by conducting a bioactivity/bioequivalence bridging study, and the Division concurred that comparability might be established by the performance of a successful bridging study.

- A number of other deficiencies, including those for CMC, Clinical, Clinical Pharmacology and Biopharmaceutics, and Pharmacology and Toxicology are also listed in the NA letter; please see the NA letter for a complete listing of these deficiencies and requests made to the Applicant.

- The Clinical and Statistical Reviewers (Dr. Fathia Gibril, M.D., M.H.Sc., and Wen-Jen Chen, Ph.D., respectively) both noted in their reviews that the clinical studies submitted to the NDA at that time supported the efficacy (and safety) of Creon for the treatment of patients with exocrine pancreatic insufficiency. However, the Clinical Reviewer recommended an Approvable (AE) action, pending resolution of the serious outstanding CMC deficiencies.

- On 20-November-2007, the Agency received the Complete Response (CR) to the NA letter for Creon (Class 2 response). During the course of the review of this CR submission, five formal Information Request (IR) letters were issued by the Division to the Applicant to obtain additional safety, efficacy, CMC, clinical pharmacology (biopharmaceutical), and regulatory information that was considered necessary for the review. In response to these IR letters, a major amendment to the CR was received on 16-March-2007, and the PDUFA goal date was extended by three months to provide time for a full review of the submission (extended user fee goal date of 17-August-2007).

The Creon® (pancrelipase delayed-release capsules) product submitted for marketing approval in this CR amendment is distinct from Creon® Minimicrospheres® submitted for marketing approval in the original NDA submission. Creon® Minimicrospheres® is the product currently marketed in the US, and was deemed Not Approvable after review of the original NDA submission in October, 2003. Creon® (pancrelipase delayed-release capsules) will also be referred to as the "new formulation" and "the to-be-marketed product" (TbMP). Creon® Minimicrospheres® will also be referred to as the "old formulation" and the "currently marketed product" (CMP). The Applicant plans to discontinue marketing of Creon® Minimicrospheres® after obtaining approval for Creon®.

Several formulations of Creon will be discussed in the review of this CR submission; however, the most important issues with the Creon formulation relate to the currently

marketed product (CMP) and the to-be-marketed product (TbMP). All of the clinical efficacy and safety studies submitted in this CR submission, and the pivotal efficacy studies conducted and submitted in the original Creon NDA were conducted with the Creon CMP. To date, no clinical efficacy and safety studies have been conducted with the Creon TbMP. Since no studies have been conducted with the Creon TbMP, and as noted in the NA letter from 2003, the Applicant was required to link the TbMP with the CMP used in clinical trials once the CMC deficiencies were corrected. In an effort to link the Creon CMP and TbMP, the Applicant conducted a bridging bioactivity/bioavailability (Bridging) study with the two formulations in support of this CR. The Bridging study is the only clinical study conducted to date in which the Creon TbMP has been administered to patients.

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

- Clinical Review: Ethan D. Hausman, M.D., dated August, 2007
- Statistical Review and Evaluation, Clinical Studies: Sonia Castillo, Ph.D., dated 17-July-2007
- Pharmacology/Toxicology Review: David B. Joseph, Ph.D., dated 25-June-2007
- Clinical Pharmacology Review: Tien-Mien Chen, Ph.D., dated 16-July-2007
- CMC (Drug Substance and Drug Product) Review: Wei Guo, Ph.D., dated 27-July-2007
- Product Quality Microbiology Review: Anastasia G. Lolas, Ph.D., dated 04-May-2007
- Virology Review: Ennan Guan, Ph.D., dated 30-July-2007
- Facility Inspection Memorandum: Michael F. Skelly, Ph.D., dated 08-June-2007
- Division of Medication Errors and Technical Support Proprietary Name Consultation Response, and Label and Labeling Review: Deveonne Hamilton-Stokes, dated 09-April-2007 and 17-April-2007, respectively

In addition, reviews performed for the initial NDA review in 2003 are also referred to in support of this CR amendment, including

- Clinical Review: Fathia Gibril, M.D., M.H.Sc., dated 24-September-2003
- Medical Officer Secondary Review: Hugo E. Gallo-Torres, M.D., Ph.D., P.N.S., dated 15-September-2003
- Division Director Summary Review: Robert L. Justice, M.D., M.S., dated 09-October-2003

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

II. Chemistry, Manufacturing and Controls

CMC data have been extensively reviewed by the Product Reviewer (Wei Guo, Ph.D.), Microbiology Reviewer (Anastasia Lolas, Ph.D.), and Virology Reviewer (Ennan Guan, Ph.D.). Please refer to the Product, Microbiology, and Virology reviews for more detailed information. Important issues identified in the Product, Microbiology, and Virology reviews are summarized as follows:

A. Product Review

The Product Reviewer's overall assessment of the CMC data submitted in this CR amendment was that the application is Approvable, and additional comments are to be sent to the Applicant.

The Product review was divided into three parts (Parts A, B and C). In Part A, the Product Reviewer reviewed the Applicant's responses to the deficiencies identified in the previous CMC review. In Part B, the new information submitted regarding new Drug Substance (DS) and modified Drug Product (DP) was reviewed. Part C contains the assessment of the information the Agency requested during this review cycle (as Information Requests sent to the Applicant). Issues identified from the Product review are summarized as follows:

The DS and DP are both manufactured by the Applicant, Solvay Pharmaceuticals Gmb H (Rübenberge, Germany). The manufacturing facility had never been inspected by the Agency at the time of this review (inspections are deferred pending resolution of outstanding CMC issues and finalization of the TbMP).

DS is derived from porcine pancreas glands harvested from pigs raised as human food. The glands are obtained from slaughter houses, (b) (4) . Characterization of the enzymes contained in the DS, including assays for amylase, lipase, protease (total and a number of individual proteases, such (b) (4)), and (b) (4) was performed.

The manufacturing process for DP is divided into (b) (4) resulting in Creon capsules of three sizes: Creon® 6, 12, 24 containing 6,000, 12,000, and 24,000 lipase units, respectively. The Applicant changed the formulation of Creon DP used in the clinical studies conducted in support of the original NDA application (Creon CMP) at the Agency's request to remove the mineral oil used in the old (CMP) formulation.

The new formulation (Creon®; TbMP) is also distinguished from the old formulation (Creon® Minimicrospheres® [MMS]; CMP) by qualitative and quantitative differences in

the excipient content. Differences in the old (CMP) and new (TbMP) formulations are summarized as follows (from Dr. Guo's CMC Review):

Table 1: Active and Inactive Ingredients in Old and New Creon Formulations

	Old Formulation (CMP)		New Formulation (TbMP)	
Ingredients	**mg/g**	**Percentage (%)**	**mg/g**	**Percentage (%)**
Active Ingredient				
Pancrelipase	(b) (4)			
Inactive Ingredients				
Polyethylene glycol 4,000 (USP)	(b) (4)			
Light mineral oil (USP)				
Hydroxypropyl methylcellulose pthalate				
Dibutyl phthalate (USP)				
Hypromellose pthalate				
Dimethicone 1,000 (USP)				
Cetyl alcohol				
Triethyl citrate				
Sum	**1000**	**100**	**1000**	**100**

(b) (4)

Creon (and all of the PEPs) are complex products that contain highly variable amounts and types of enzymes (such as lipase, amylases, and proteases), given their derivation from porcine pancreata and the inherent variability of the source material. It was the assessment of the CMC review team that comparability of the old (CMP) and new (TbMP) formulations could not be demonstrated by CMC evaluation, and comparability would have to be demonstrated by clinical measures. Thus, no CMC comparability analyses between the old and new formulations were assessed as part of the CMC review.

The specific deficiencies identified in the Product review are listed as follows (from Dr. Guo's Review):

- Due to the critical role of (b) (4) activity in lipase activity, adequate control of (b) (4) activity must be ensured in the DS and DP. It is recommended that the measurement of lipase potency in release and stability testing be performed in both the absence and presence of excess exogenous (b) (4), and that the acceptance criteria for activity under each assay condition be established and justified.

- The olive oil used as lipase substrate has an acceptance criterion of (b) (4) at (b) (4) of the total fatty acids, but the testing results of the nine batches have (b) (4) varying from (b) (4) of total fatty acids. It is recommended that the acceptance criteria of (b) (4) be adjusted to ensure that a consistent substrate is used in the lipase potency measurements.

- Dissolution testing of DP should be performed on intact capsules.

- The acceptance criterion of the HPLC identity test used for DS and DP is to be defined.

- The DS and DP release test sampling plans are to be provided.

- The acceptance criterion of lipase activity for individual capsules was changed to (b) (4) of the label claim on and after page 0151 of volume 1, submission dated March 21, 2007. This is inconsistent with the proposed acceptance criteria of (b) (4) of label claim on pages, 0118, 0131, 0134, and 0137 of the same submission. The Applicant is asked to address this inconsistency.

- Information on the manufacturer and specifications of container, closure, and seals for DS packaging should be provided. Representative certificates of analysis for the seals used in DS container/closure system are to be provided.

- DP labeling has been proposed as (b) (4) The length of time that excursions in temperature are permitted is to be specified.

These issues are to be communicated to the Applicant as part of the Approvable letter.

B. Microbiology Review

The Microbiology Reviewer recommended an Approval action.

Dr. Lolas noted that the product was non-sterile, and a microbial limits in-process test performed before blending on each batch of unblended pellets for total aerobic microbial count was not more than (b) (4) total combined yeasts and molds count was not more than (b) (4) *Salmonella* was absent/10 g, and *Escherichia coli* was absent/1 g. Overall, the analytical procedures, validation of analytical procedures, and stability were found to be acceptable, and no microbiology deficiencies were identified in the review.

The Microbiology Reviewer noted that one comment should be communicated to the Applicant, as follows:

(b) (4)

C. Virology Review

Virology issues identified from the Virology review are summarized as follows:

The active pharmaceutical ingredient in Creon, pancrelipase, is derived from native pig pancreas tissue. One batch of pancrelipase DS requires glands from several thousand pigs, and such a large quantity of raw material has to be obtained from by-products of slaughtered pigs intended for use as food (these pigs have been certified as fit for human consumption). For this reason, the possibility of contamination of the starting material with viruses relevant to swine has to be considered. The viruses known to be present in swine

include enveloped, non-enveloped, and emerging viruses listed and considered in detail in Dr. Guan's review.

(b) (4) viral inactivation steps are involved in the Applicant's manufacturing process, (b) (4) Viral clearance studies are then performed as part of the manufacturing process. (b) (4) The ability of these steps to kill viruses is evaluated by a viral spiking study using model viruses selected to cover an appropriate range of viruses of concern for pancrelipase. Per Dr. Guan's review, the manufacturing process demonstrated an effective inactivation for enveloped viruses, and acceptable results for non-enveloped viruses of concern, except for porcine parvovirus (PPV) and feline calicivirus (FCV).

The Applicant established a risk management plan whereby routine monitoring employing Q-PCR assays to detect potentially zoonotic porcine viruses that may not be inactivated by the manufacturing process was established. The virological monitoring covers the potentially zoonotic, non-enveloped viruses including: Hepatitis E virus (HEV), encephalomyocarditis virus (EMCV), swine vesicular disease virus (SVDV), and rotavirus A (Rota V A). If Q-PCR is positive, then batches will be re-evaluated by a cell-based infectivity assay. The reported results of this routine viral testing by Q-PCR from September 2002 to April 2003, and for all batches (total of 62) tested from June 2005 to March 2006 were negative for the detection of these viral genomes. Dr. Guan assessed the risk assessment and risk management as adequate.

The overall assessment by the Virology Reviewer is that the Applicant's pancrelipase appears to adequately address enveloped and non-enveloped viral safety, except for PPV. The following comments are to be communicated to the sponsor:

"Since infections PPV particles presented in the product, we recommend that the sponsor set the specification for infectious PPV particles for the DS and final DP, alternately setting an action limit is acceptable. Although the pancrelipase manufacturing demonstrated an effective inactivation of enveloped viruses, but not removal of viruses, it would be very useful if the (Applicant) can provide enveloped viral load by PCR-based testing for their process intermediates to estimate the genomic equivalents."

III. Nonclinical Pharmacology and Toxicology

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

PEPs have been widely used in clinical practice as treatments for EPI since prior to 1938, and there is a large amount of clinical experience with these products in human patients. Creon has been available for commercial use in the US since 1987, and has marketing authorizations in approximately 70 countries worldwide. Per the Guidance, given the long history of clinical use of Creon (and the drug substance), the performance of new animal

pharmacology studies with the active ingredient (pancrelipase) is not needed to support the Creon clinical development program. However, toxicology studies are needed if the excipients in the Creon DP are not classified as GRAS, and the toxicology program for the excipients should supply data from long-term studies in both rodent and non-rodent mammalian species, plus standard reproductive toxicity and genotoxicity information.

Consistent with the Guidance, pharmacology and toxicology studies in this CR amendment were limited to the evaluation of the excipient breakdown product O-phthalic acid (also known as phthalic acid). The presence of phthalic acid in Creon is due to degradation of the excipient hydroxypropyl methylcellulose phthalate, and the amount of phthalic acid present was shown to increase during storage of the drug product. The data for phthalic acid were submitted under IND 47,546, and include:

1. The results of a four-week, oral toxicity study of phthalic acid in rats, conducted to evaluate the potential for adverse effects due to phthalic acid ingestion associated with Creon administration; and

2. A summary report of toxicological information on phthalic acid and closely related compounds.

Dr. Joseph's review was limited to the review of these data, and important issues identified in the review are summarized as follows:

- The safety assessment of phthalic acid intake associated with Creon administration is based on an estimated maximum dose of 21,000 lipase units (U)/kg/day (6,000 U/kg/meal, 3.5 meals/day). The maximum dose of phthalic acid from this Creon administration is estimated to be 13 mg/kg/day.

- In the four-week oral toxicity study in rats, the tolerated dose of phthalic acid was 250 mg/kg/day, which exceeds the estimated maximum dose level of phthalic acid by 19-fold. Therefore, the four-week oral toxicity study provides a reasonable assurance of safety for Creon with respect to phthalic acid intake. Dr. Joseph commented that since Creon will be used as a long-term therapy given the irreversible nature of EPI, a chronic toxicity study of at least six months duration would have been more useful of the assessment of the safety of phthalic acid intake; however, the four-week study was consistent with ICH guidelines (ICH Guidance Q3B(R)).

- Oral administration of phthalic anhydride produced no neoplastic or non-neoplastic changes in a two-year carcinogenicity study in rats, and the survival of treatment groups was unaffected. The results of this study are considered to be representative of the effects of lifetime exposure to phthalic acid, because phthalic anhydride is converted to phthalic acid in water or biological fluids.

- Exposure to other excipients in Creon, such as PEG and cetyl alcohol (see listing of excipients in Table 1 in CMC Product Review section above), were felt to be

within the levels of these excipients found in other approved oral formulations, and are not considered to be a safety concern. Creon also contains gelatin and several minor excipients that are present in the capsule shell and imprinting ink. Potential exposure to these excipients is likely to be small, and they are also not considered to be a safety concern.

- Specific labeling wording changes were recommended. However, as this CR amendment is recommended to receive an Approvable action, no labeling changes are being negotiated at this time (please see Dr. Joseph's review for the specific labeling wording recommendations).

Dr. Joseph's overall conclusion was that, based on the results of the submitted studies and the summary report (of other preclinical studies of o-phthalic acid), the estimated maximum dose of o-phthalic acid resulting from Creon administration is not considered to be a safety concern, and an Approval action was recommended.

IV. Clinical Pharmacology

The clinical pharmacology data have been extensively reviewed by the Clinical Pharmacology Reviewer (Tien-Mien Chen, Ph.D.). Please refer to this review for more detailed information. Clinical pharmacology information submitted to the CR amendment was limited to the results obtained in a single, bioactivity/bioequivalence (Bridging) study, and Dr. Chen's review was limited to the review of this study. As required by the NA letter of 2003, this Bridging study was conducted in an effort to link the Creon TbMP to the Creon CMP.

The Bridging study was a single-center, randomized, double-blind (DB), 2X2 cross-over, duodenal intubation study that compared the duodenal lipase activity of Creon TbMP to Creon CMP. In each of two study treatment periods and after an overnight fast, patients received a meal with a dose of Creon TbMP or CMP, and then underwent continuous duodenal aspiration over a three-hour period to measure pancreatic lipase activity from the aspiration specimens. Fifteen patients were entered in the study, and nine patients completed both phases of the study. Important issues identified in the review of this study are summarized as follows:

- High inter-subject variability was observed for both the Creon TbMP and CMP. Ten patients had values that were higher than the administered dose of 60,000 lipase units (almost four-fold the administered dose). Conversely, two patients had little or no lipase activity measured in their duodenal aspiration samples. These observations rendered the study unreliable as a tool to establish comparability between the two formulations.

- An inspection of the study site was also conducted by the Division of Scientific Investigations (DSI), which noted that this study was not reliable as performed (please see Section VI Clinical Site Inspections, below, for additional information).

Dr. Chen's overall conclusion, based on the results of the Bridging study, is that the Applicant has not demonstrated that the Creon TbMP is comparable to the Creon CMP. Thus, the efficacy and safety results obtained from the clinical efficacy and safety studies conducted with the Creon CMP cannot be used to establish the efficacy and safety of the Creon TbMP.

V. Clinical/Statistical

The clinical data have been extensively reviewed by the Clinical Reviewer (Ethan D. Hausman, M.D.) and the Statistical Reviewer (Sonia Castillo, Ph.D.). In addition, the Clinical Review performed for the original NDA submission in 2003 (by Fathia Gibril, M.D., M.H.Sc., dated 24-September-2003), the Secondary Clinical Review (by Hugo E. Gallo-Torres, M.D., Ph.D., P.N.S., dated 15-September-2003), and the Division Director Summary Review (by Robert L. Justice, M.D., M.S., dated 09-October-2003) were also used in support of this CR amendment. Please refer to the Clinical and the Statistical Reviews for more detailed information.

A. Clinical Studies

The CR amendment contains efficacy and safety information from a total of 57 clinical studies performed with Creon; however the most important studies submitted were two new short-term efficacy and safety studies submitted in this CR amendment. Both studies were conducted with Creon CMP. The two new short-term efficacy and safety studies are:

1. Study S248.3003 (Infant CF Study): an eight-week, non-randomized, open-label, uncontrolled, single-arm, short-term safety and efficacy study of Creon CMP in twelve infants with CF, ages one to 24 months.

2. Study S245.3.115 (Adult EPI Study): a multi-center, randomized, double-blind (DB), placebo-controlled, 13-day, parallel-group, efficacy and safety study of Creon CMP in 94 adult patients, ages 20 years or older, with EPI due to CP or pancreatectomy.

The Clinical Reviewer (Dr. Hausman) extensively reviewed these two studies in the Primary Clinical Review, and the Statistical Reviewer (Dr. Castillo) conducted statistical analyses of both these studies. In addition, Dr. Hausman summarized findings from the original NDA review (by Dr. Gibril) for three pivotal short-term efficacy and safety studies with Creon CMP, in which the efficacy (and safety) of Creon CMP in the treatment of steatorrhea due to EPI was assessed as having been established. These three studies were also conducted with Creon CMP, and are:

3. Study S223.2.101 (Pediatric CF Study): a multi-center, randomized, DB, placebo-controlled, efficacy and safety study of Creon CMP in 38 pediatric patients with CF, ages seven to 17 years. Patients randomized to Creon CMP treatment received up to seven days of Creon in the DB period of this study.

4. Study S223.2.102 (Adult CF Study): This study was of the same design as the Pediatric CF Study, except that the patients were adults (n=36) with CF, ages 18 years and older.

5. Study S223.2.01 (Adult CP Study): a randomized, DB, placebo-controlled, efficacy and safety study of Creon CMP in 27 adult patients with CP, ages 38 to 74 years. Patients randomized to Creon CMP treatment received up to two weeks of Creon in the DB period of this study.

Thus, a total of five short-term efficacy and safety studies were used to describe the efficacy (and safety) of Creon CMP.

The remaining studies (approximately 50 studies) were unsuitable for substantive review due to study design (e.g., uncontrolled, open-label) or as they were conducted with older formulations of Creon that are no longer marketed. Most of the information contained in these remaining studies was summarized in the safety update, and only provides supportive safety information for Creon.

It is noted that all five of the studies used to describe Creon's efficacy profile were conducted with the Creon CMP formulation. To date, no short-term clinical efficacy and safety studies have been conducted with Creon TbMP, with the exception of single-dose Creon TbMP administration in the Bridging study. However, since the Bridging study did not establish the comparability of Creon CMP and TbMP, the efficacy and safety of Creon TbMP has not been described.

B. Efficacy Results

The primary efficacy endpoint in the five efficacy studies was the comparison of percent coefficient of fat absorption (%CFA) to a %CFA on no-treatment (or placebo). %CFA is determined from a 72-hour stool collection (usually while the patient is consuming a high-fat diet) and is calculated by:

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

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

The two new short-term efficacy and safety studies (Infant CF Study and Adult EPI Study) submitted in this CR amendment are summarized as follows:

1. Study S248.3003 (Infant CF Study)

The Infant CF study was a non-randomized, open-label, uncontrolled, single-arm, short-term safety and efficacy study of Creon CMP in infant patients with CF. Creon CMP was administered at a dose of 2,000 lipase units per gram of fat intake per day (administered with meals) for eight weeks. In this study, all patients underwent a seven- to ten-day no-treatment period (Baseline), followed by an eight-week period of Creon CMP treatment. Primary efficacy was evaluated by change from Baseline in CFA compared to CFA during Creon treatment after two weeks of Creon treatment. Patients were eligible for participation in the active-treatment phase of the study if they had a Baseline CFA of less than or equal to 70%.

Twelve infants with CF (five males, seven females), ages one to 23 months at study entry, were enrolled and treated with Creon. All 12 patients completed the study and were included in the ITT population. Mean Baseline CFA was 58% (range 5 to 71%), and mean CFA on treatment was 85% (range 54 to 99%). The result for the primary endpoint of mean change in CFA from Baseline at Week 2 was 27% (range -9 to 80%; 95% C.I. [12.9, 40.4]). The Statistical Reviewer assessed this result as not statistically supportive as the study was not of adequate size to draw statistical inferences; however, this result appears to show a clinically meaningful increase in CFA, and is suggestive of a benefit of Creon treatment in infant patients with CF.

An additional unplanned subgroup analysis was performed for the primary endpoint, whereby change from Baseline in CFA was evaluated in the subgroups of patients with Baseline CFA <60% (moderate to severely affected patients) and ≥60% (less severely affected patients). The results show that for the patients with Baseline CFA <60% (n=4), mean Baseline CFA was 41% (range 5 to 58%), mean CFA with treatment was 84% (range 77 to 95%), and mean change in CFA was 43% (range 22 to 80%; 95% C.I. [-0.9, 86.1]). For patients with Baseline CFA ≥60% (n=8), mean Baseline CFA was 66% (range 61 to 71%), mean CFA with treatment was 85% (range 54 to 99%), and mean change in CFA was 19% (range -9 to 38%; 95% C.I. [6.8, 30.6]). As expected, the subgroup analysis showed that the more severely affected patients (by Baseline CFA) had greater increases in CFA with Creon treatment than the less severely affected patients. Although these results are suggestive of the clinical benefit of Creon treatment, especially in the more severely affected patients at Baseline, given the small numbers of patients in each of the subgroups, no definitive conclusions can be drawn from these results.

The results of the primary efficacy analysis and the subgroup analyses are summarized in the following table (summarized from Dr. Hausman and Dr. Castillo's reviews):

Table 2: Infant CF Study, Change from Baseline in CFA

Population	ITT Population	Baseline CFA <60%	Baseline CFA ≥60%
N =	12	4	8
Baseline CFA, mean (%)	58	41	66
Treatment CFA, mean (%)	85	84	85
Mean change from Baseline in CFA (95% C.I.)	27 (12.9, 40.4)	43 (-0.9, 86.1)	19 (6.8, 30.6)

The results for change in CFA from Baseline at Week 2 of Creon treatment did not show a statistically significant benefit for Creon treatment overall, or in either subgroup, likely due to the small size of the study. However, these results were felt to be clinically meaningful, and are suggestive of a benefit to Creon treatment in infant patients with CF, especially for the more severely affected patients at Baseline. The results are also consistent with results previously obtained in adult and pediatric patients (ages seven years and older) with EPI due to CF (or other causes), and do not suggest that infants treated with Creon respond differently (by short-term efficacy measures) than do older patients. Thus, these results can be considered supportive of Creon administration to patients with CF as young as one month of age for the treatment of EPI.

2. Study S245.3.115 (Adult EPI Study)

The Adult EPI study was a randomized (1:1:1), DB, placebo-controlled, parallel-group, short-term, safety and efficacy study conducted in Japan. The study evaluated the administration of Creon CMP to adult patients, ages 20 years or older, with EPI due to CP or pancreatectomy (PY). Patients randomized to Creon received Creon CMP at a dose of either 1.5 g/day (60,000 lipase U/day; low-dose) or 3.0 g/day (120,000 lipase U/day; high-dose) for up to 13 days. In this study after completion of the Screening period, all patients underwent five days of single-blind placebo treatment to establish a Baseline CFA. Then, only patients with a Baseline CFA less than 80% were randomized into one of the three treatment groups to receive seven days of DB treatment with either placebo, low-dose Creon, or high-dose Creon. Primary efficacy was evaluated by comparing the mean change in CFA from Baseline (single-blind placebo treatment) to CFA after seven days of DB treatment for the placebo group compared to the two Creon treatment groups.

One-hundred fifty-six (156) patients were screened and underwent the single-blind placebo phase of the study. Of these 156 patients, 95 patients qualified for randomization (by Baseline CFA <80%). One patient withdrew prior to randomization, leaving 94 patients who were randomized into the DB phase of the study: 30 patients to the placebo group, 31 patients to the low-dose Creon group, and 33 patients to the high-dose Creon group. Ninety-three (93) patients were included in the ITT population. Baseline demographic data showed that, overall, the three treatment groups were relatively well-balanced by Baseline demographic criteria. Eight-one percent (81%) of patients were male, 100% were Asian, mean age was 63 years, and 35 (37%) had a history of CP and 59 (63%) had a history of pancreatectomy.

The results for the primary efficacy endpoint show that mean Baseline (single-blind placebo) CFA for the three DB treatment groups were similar (55%, 67%, and 68% for the placebo, low-dose Creon, and high-dose Creon groups, respectively). Mean change from Baseline after DB treatment was 4% in the placebo group, 11% in the low-dose Creon group, and 16% in the high-dose Creon group. Mean CFA change from Baseline compared to the placebo group for the low-dose Creon group was 7% (P = 0.144), and for the high-dose Creon group was 12% (p = 0.015). The results were significant only for the comparison of mean change from Baseline in the high-dose Creon group versus the group placebo.

A subgroup analysis of the primary endpoint was performed, where the results by subgroup of patients with CP or PY were analyzed for mean change in CFA from Baseline to DB treatment for the placebo group compared to the two Creon groups. For the CP subgroup (n=34), mean Baseline CFA for the three DB treatment groups were somewhat imbalanced, and were 57% in the placebo group, 70% in the low-dose Creon group, and 78% in the high-dose treatment. Mean change from Baseline after DB treatment was 5% in the placebo group, 9% in the low-dose group, and 7% in the high-dose group. Mean CFA change from Baseline compared to the placebo group for the low-dose Creon group was 4% (p = 0.540), and for the high-dose group was 2% (p = 0.781). These results were neither statistically significant nor clinically meaningful for either Creon treatment group. The imbalance between the treatment groups by mean Baseline CFA may have affected the results. Since the placebo group had the lowest baseline CFA and the high-dose group had the highest CFA, this imbalance could have resulted in a decreased likelihood of detecting a difference between the placebo and high-dose Creon group, as the high-dose group had a lower capacity to respond to active treatment.

For the PY subgroup (n = 58), mean Baseline CFA for the three DB treatment groups were similar, and were 54%, 66%, and 62% in the placebo, low-dose Creon, and high-dose Creon groups, respectively. Mean change from Baseline after DB treatment was 3% in the placebo group, 12% in the low-dose Creon group, and 20% in the high-dose treatment group. Mean CFA change from Baseline compared to the placebo group for the low-dose Creon group was 9% (p = 0.180), and for the high-dose group was 18% (p =0.011).

The results of the primary efficacy analysis and the subgroup analyses are summarized in the following table (summarized from Dr. Hausman and Dr. Castillo's reviews):

Table 3: Adult EPI Study, Change from Baseline in CFA

Treatment Group	Placebo	Low-dose Creon (1.5 g/d)	High-dose Creon (3.0 g/d)
Overall			
N=	30	30	33
Baseline CFA, mean (%)	55	67	68
Mean Change in CFA from Baseline (%)	4	11	16
Mean Treatment Difference vs. Placebo	-	7	12
p-value for Mean Treatment Difference*	-	0.144	0.015
Subgroup Analyses			
Chronic Pancreatitis (CP)			
N=	12	11	11
Baseline CFA, mean (%)	57	70	78
Mean Change in CFA from Baseline (%)	5	9	7
Mean Treatment Difference vs. Placebo	-	4	2
p-value for Mean Treatment Difference*	-	0.540	0.781
Pancreatectomy (PY)			
N=	18	19	21
Baseline CFA, mean (%)	54	66	62
Mean Change in CFA from Baseline (%)	3	12	20
Mean Treatment Difference vs. Placebo	-	9	18
p-value for Mean Treatment Difference*	-	0.180	0.011

* For Creon groups compared to placebo group for mean difference in CFA from Baseline to DB treatment

Problems with the conduct of the study were noted by both the Clinical and Statistical Reviewers. The Applicant conducted an interim analysis during the study that was not prespecified, and it appeared that the analysis was unblinded. Based on the results of the interim analysis, the sample size was increased from 18 to 25 patients per treatment arm. It was also noted by the Clinical Reviewer that after the interim analysis, a higher percentage of more severely affected PY patients were enrolled than prior to the interim analysis, which likely resulted in a change in the overall results for the study in favor of detecting a treatment effect (as more severely affected patients have a greater capacity to respond to treatment). The Clinical and Statistical Reviewers both concluded that the unplanned analysis rendered the final analyses for this study uninterpretable, and the results cannot be used to support the efficacy of Creon CMP for the treatment of EPI due to CP or PY.

3. Summaries for the Three Previously Reviewed Pivotal Efficacy Studies

a) Pediatric CF Study

The Pediatric CF Study was a multi-center, randomized, DB, placebo-controlled, efficacy and safety study of Creon CMP in 38 pediatric patients with CF, ages seven to 17 years. Patients randomized to DB Creon CMP treatment received up to seven days of Creon. In this study, all patients underwent a two- to three-week open-label (OL) Creon treatment phase, followed by a five- to seven-day DB treatment phase where patients were randomized to treatment with placebo or Creon (randomized withdrawal). At the end of the OL Creon treatment phase, Baseline CFA was determined, and patients with a Baseline CFA greater than 80% were eligible for randomization into the DB treatment phase. The primary efficacy endpoint was the comparison of mean change in CFA from Baseline to DB treatment between the DB placebo and Creon treatment groups.

The results showed that the DB placebo-treatment group had a mean decrease in CFA of 37% from Baseline, and the mean CFA for the DB Creon-treatment group was essentially unchanged from Baseline (mean change of -3%). The overall results show a statistically significant and clinically meaningful difference in mean change in CFA between the two groups of 35% ($p < 0.001$) in favor of Creon treatment. The Clinical Review Team assessed the results as having shown evidence of a benefit for Creon in the treatment of steatorrhea in pediatric patients with CF, ages seven to 17 years.

b) Adult CF Study

The Adult CF Study was of the same design as the Pediatric CF Study, except that the patients were adults with CF, ages 18 years and older (n=36).

The results showed that the DB placebo-treatment group had a mean decrease in CFA of 35% from Baseline, and the mean CFA for the DB Creon-treatment group was essentially unchanged from Baseline (mean change of -2%). The overall results show a statistically significant and clinically meaningful difference in mean change in CFA between the two groups of 32% ($p < 0.001$) in favor of Creon treatment. The Clinical Review Team assessed the results as having shown evidence of a benefit for Creon in the treatment of steatorrhea in adult patients with CF, ages 18 years or older.

c) Adult CP Study

The Adult CP Study was a randomized, DB, placebo-controlled, efficacy and safety study of Creon CMP in 27 adult patients with CP, ages 38 to 74 years. Patients randomized to DB Creon CMP treatment received up to two weeks of Creon. In this study, all patients underwent a two-week, single-blind (SB) placebo-treatment phase, followed by a five- to seven-day DB treatment phase (Creon or placebo). At the end of the SB placebo-treatment phase, Baseline CFA was determined, and patients with a Baseline CFA less than 80% were eligible for randomization into the DB treatment phase. The primary efficacy endpoint was the comparison of mean change in CFA from Baseline to DB treatment between the DB placebo and Creon treatment groups.

The results show that the DB placebo-treatment group had a mean change in CFA of 12% from Baseline, and the DB Creon-treatment group had a mean change in CFA of 37%. The overall results show that the DB Creon group had a larger mean increase in CFA compared to the DB placebo group that was clinically meaningful and statistically significant (p=0.0185). The Clinical Review Team assessed the results as having shown evidence of a benefit for Creon in the treatment of steatorrhea in adult patients with CP.

4. Efficacy Conclusions

The efficacy findings from the five Creon CMP short-term efficacy and safety studies, either newly reviewed in this CR amendment or summarized from the original Creon CMP NDA submission, show that:

- The treatment of pediatric and adult patients with CF (ages seven years and older), and adult patients with CP with Creon CMP results in a statistically significant and clinically meaningful benefit to patients, as shown by mean increases in CFA as compared to placebo treatment.

- The treatment of infants with CF, ages one to 24 months, with OL Creon CMP showed clinically meaningful increases in CFA compared to a no-treatment Baseline showed a trend toward statistical significant. Significance was likely not reached due to the small number of patients treated in this study (n=12). Subgroup analysis showed that more severely affected patients (those with CFA less than 40% at Baseline) had the greatest increases in CFA on treatment. The results in this study were consistent with results seen with Creon CMP treatment in older pediatric and adult patients with CF (ages seven years and older), and are supportive of labeling of Creon for the treatment of steatorrhea in infants with CF, ages one month and older.

- The results of the Adult EPI study cannot be used to support the effectiveness of Creon CMP in the treatment of EPI due to problems with study conduct, and because the results of the study were not clinically meaningful.

Overall, these efficacy findings support the labeling of Creon CMP for the treatment of steatorrhea due to EPI from CF or other causes, in infants, pediatric, and adult patients, ages one month and older. However, all of the clinical efficacy and safety studies were

conducted with Creon CMP, and no studies (with the exception of the Bridging study) have been conducted with Creon TbMP. Since the Bridging study failed to demonstrate the clinical comparability of the Creon CMP and Creon TbMP formulations, the clinical efficacy (and safety) results for the Creon CMP cannot be used to support the approval of Creon TbMP. Thus, the effectiveness of Creon TbMP for the treatment of steatorrhea in patients with EPI has not been demonstrated, and the information submitted in this CR amendment does not support the approval of Creon TbMP.

C. Safety Results

1. Background

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

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

One exception to the relative safety of the PEPs is the association of fibrosing colonopathy with PEP use. Fibrosing colonopathy associated with PEP use is rare, and although the etiology has not been completely elucidated, it has been assumed to be related to high or inappropriate dosing of PEPs. Thus, the Cystic Fibrosis Foundation (CFF) in conjunction with the FDA have recommended that PEP doses not exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal (FitzSimmons et al., 1997[3]; Borowitz et al., 2002[4]). Since publication of these recommendations, cases of fibrosing colonopathy have been reported only sporadically, and are unlikely to be reported during the relatively small clinical trials conducted in support of the PEP NDAs. Thus, continued monitoring for fibrosing colonopathy associated with PEP use is likely to best be performed through global safety surveillance.

Consistent with the Guidance, the safety evaluations performed for the Creon clinical development program focused predominantly on the monitoring of clinical signs and

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

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

symptoms (i.e., AE assessments) during the short-term clinical efficacy and safety studies conducted with Creon, and no long-term safety studies were performed.

2. Safety Review

The safety information submitted in this CR amendment includes an Integrated Summary of Safety (ISS), which was a Safety Update to the previous ISS submitted as part of the original NDA. Safety information from individual clinical studies conducted with Creon, and additional information from spontaneously reported commercial-use safety surveillance were included in the ISS. This safety experience includes exposure to a number of different Creon formulations (e.g., Creon MS, Creon MMS), some of which are no longer marketed.

The Safety Update contains safety information from 57 clinical studies (conducted between July 1985 and May 2006), the majority of which were open-label and uncontrolled. The safety data collected in these studies consist predominantly of AEs, which were compiled into an AE dataset that was amenable to review. Complete study reports (and safety datasets) were also submitted in this CR amendment for two new studies (Infant CF and Adult EPI Studies), and a substantive safety review was able to be conducted for these studies by the Clinical Reviewer. Safety datasets for four individual pediatric studies (Infant CF Study, Pediatric CF Safety Study [S246.3105], Prior Infant CF Safety Study [S245.3118], and Prior Young Adult CF Safety Study [K245.5004]) were also amenable to review, and were reviewed in detail by the Clinical Reviewer.

The total patient exposure included in the Safety Update was approximately 2,400 patients, approximately 1,500 of whom were exposed to Creon (any formulation), 600 to placebo, and 300 to other PEPs. The majority of patients exposed to Creon were administered Creon for eight weeks or less (approximately 75% of patients), and almost all were administered Creon for 26 weeks or less (97%). Approximately half of the patients in clinical trials were CF patients, with most of the remaining patients having EPI due to a variety of causes (mostly CP and pancreatectomy). About 60% of patients in clinical trials were male, and about 70% were Caucasian. The age ranges of patients administered Creon ranged from one month of age to more than 65 years, with infant, pediatric, adolescent and adult patients all having been represented in clinical studies, and approximately half of the Creon-treated patients were less than 18 years of age.

3. Results

The Adverse Event (AE) profile of Creon in the Safety Update, and in the review of the individual study datasets was consistent with the currently described AE profile of Creon (and other PEPs) in the medical literature. In general, reported AEs tended to reflect underlying disease, and were similar in types and frequencies to the AEs reported by placebo-treated patients. Serious and severe AEs also tended to be attributed to the underlying conditions of the patients. No new or unexpected AEs were noted during the safety review.

Review of the Safety Update dataset by the Clinical Reviewer showed that, as expected, AEs were most commonly reported in the Gastrointestinal, Infections and Infestations, and

Respiratory systems. The most commonly reported AEs by Preferred Term were: abdominal pain (by 16% of patients), headache (14%), cough and diarrhea (9% each), vomiting (7%), nausea (6%), pyrexia and flatulence (5% each). Review of the individual studies and the four Pediatric studies datasets revealed similar AE profiles in these studies, except that for the pediatric patients, as almost all of these patients had CF, respiratory and infectious AEs were somewhat more common in the pediatric populations than in the adult non-CF populations.

A total of 18 deaths were reported in the ISS, which included patients in clinical trials and deaths reporting in commercial-use safety surveillance. There were 15 deaths in Creon treated patients and three deaths in placebo-treated patients. For 14 of the 18 deaths for which a cause of death was reported, all were attributed to underlying disease (e.g., progression of cancer or cardiopulmonary disease), and did not appear to be due to administration of Creon. Similar findings were noted for Serious Adverse Events (SAEs) noted in clinical trials, with SAEs being almost entirely attributed to underlying disease. No cases of fibrosing colonopathy were reported in the Safety Update.

Overall, no new or notable safety signals were identified in the review of the safety data submitted in the CR amendment. As previously stated, however, no short-term safety and efficacy studies were conducted with the Creon TbMP. Since the Bridging study failed to establish the comparability of the Creon CMP and TbMP, the safety results obtained with Creon CMP cannot be used to definitively establish the short-term safety profile of Creon TbMP, although the Creon CMP safety data would be considered supportive of the larger Creon safety experience.

D. Clinical Conclusions and Recommendations

The Clinical Reviewer concluded that this CR amendment does not provide evidence of short-term efficacy and safety for the Creon TbMP. No clinical safety and efficacy studies have been conducted to date with the Creon TbMP, and the Bridging study did not establish comparability between the Creon CMP and TbMP. Thus, the Clinical Reviewer recommended an Approval action for this CR amendment, and comments to the Applicant should state that evidence of short-term clinical efficacy and safety with the TbMP is needed to support the approval of the Creon TbMP.

VI. Clinical Site Inspections

One clinical site inspection was performed by the Division of Scientific Investigations (DSI) as part of the review of this CR amendment. This inspection was of the clinical site that conducted the bioactivity/bioavailability (Bridging) study, which was performed at a single clinical site in Marseilles, France. Important issues identified during this clinical site inspection are summarized as follows (please see the Facility Inspection Memorandum, by Michael, F. Skelly, Ph.D. for more detailed information on the results of this inspection):

- "The inspection could not confirm the identity of the pancrelipase products dosed to subjects on each occasion."

- "The analytical method validations and quality control programs failed to demonstrate the performance of the analytical methods before and during the study. All of the normalized study endpoints are compromised by the lack of raw data for the PEG 4000 method validation, calibration, and quality control."

Thus, the Bridging study is not felt to be reliable as performed, and cannot be used to provide evidence of comparability between the Creon CMP and TbMP.

VII. Advisory Committee

An Advisory Committee was not convened for this application.

VIII. Trade Name Review

A review of the trade name "Creon", including Creon® 6, Creon® 12, and Creon® 24 was performed by the Division of Medication Errors and Technical Support (DMETS), Office of Surveillance and Epidemiology (OSE). Please see the complete consultation (by Deveonne Hamilton-Stokes) for more detailed information.

Important issues identified in the consultation are summarized as follows:

- The proprietary name Creon is acceptable from a promotional perspective, and DMETS believes that the potential for confusion with other currently marketed products is minimal.

- DMETS does not recommend the proposed names Creon 6, Creon 12, and Creon 24, as the numerical modifiers 6, 12, and 24 may be misinterpreted as dosage or days of supply. To avert the potential for errors, DMETS recommends that the Applicant revise the names of Creon 6, Creon 12, and Creon 24 to Creon 6,000, Creon 12,000, and Creon 24,000, respectively.

- Potential for confusion exists if the old Creon formulation is co-marketed with the proposed formulation, and DMETS recommended that Creon 5, Creon 10, and Creon 20 be removed from the market once Creon 6, 12, and 24 are approved.

These issues were communicated to the Applicant during the review cycle. In additional communications with the Applicant, the Applicant agreed to change the proposed proprietary names to Creon 6,000, Creon 12,000, and Creon 24,000. The Applicant additionally submitted a plan to remove the old Creon 5, 10, and 20 from the market once approval for the new Creon 6,000, 12,000, and 24,000 is obtained, so that these two products would not be co-marketed.

IX. Pediatrics

Creon is currently in use by pediatric patients, the majority of whom have CF, and the Applicant intends to continue marketing Creon to pediatric patients should Creon receive

NDA approval. A recent CF consensus statement[4] recommends that all pediatric patients with CF be treated with PEPs as soon as CF is diagnosed, which would include the treatment of infants. Therefore, the evaluation of the safety and efficacy of Creon in children from infancy through adolescence in clinical trials is considered to be necessary for the adequate assessment of this product.

The overall Creon clinical development program has included pediatric patients in clinical studies, predominantly in short-term, open-label, uncontrolled studies with several different Creon formulations, and about half of the 1,500 Creon-treated patients included in the ISS were less than 18 years of age. Exposure to Creon by age group is as follows (from Dr. Hausman's review, summarized from estimated patient exposure in the ISS, numbers are approximates):

- Ages less than four years: 85 patients (6% of Creon-treated patients in the ISS)
- Ages four to 12 years: 450 patients (30%)
- Ages 12 to 18 years: 250 patients (17%)

The efficacy of Creon CMP in the treatment of pediatric patients (seven to 17 years of age) was demonstrated in the original NDA review in the Pediatric CF study, where evidence of a benefit for Creon in the treatment of steatorrhea in pediatric patients with CF, ages seven to 17 years, was shown (by an increase in CFA as compared to placebo). The NA letter for the original NDA requested that the Applicant study Creon administration to patients younger than seven years of age, and the Infant CF Study, where 12 infants with CF, ages one to 24 months, underwent short-term efficacy and safety evaluation in a clinical study, addressed this request. In the Infant CF Study, the results were consistent with the results seen with older pediatric and adult patients with CF, did not suggest that infants treated with Creon respond differently than do older patients, and are supportive of Creon administration to patients with CF as young as one month of age, for the treatment of steatorrhea.

Thus, children from infancy through adolescence appear to have been adequately studied with Creon CMP; however, these studies were all conducted with the Creon CMP, and do not support the short-term efficacy and safety of Creon TbMP in pediatric patients.

X. Discussion

This CR amendment provides additional short-term efficacy and safety data in patients as young as one month of age for Creon CMP, and provides additional short-term safety information for Creon CMP. The Applicant has also addressed many of the CMC issues from the original NDA application that lead to the NA decision for Creon CMP in 2003. However, the newly formulated Creon TbMP is a distinct product from Creon CMP, and the Applicant has failed to demonstrate any evidence of the safety and efficacy of the Creon TbMP. No clinical efficacy and safety studies have been conducted to date with the Creon TbMP, and the Bridging study failed to demonstrate the clinical comparability of the Creon CMP and TbMP. Thus, the data contained in this CR amendment are insufficient to support the approval of the CR amendment and of the Creon NDA.

XI. Regulatory Conclusions

This Reviewer recommends that this CR submission receive an Approvable action.

No clinical efficacy and safety studies have been performed to date with the Creon TbMP. Efficacy and safety have previously been demonstrated with the Creon CMP; however, the Applicant was not able to establish the clinical comparability of the Creon CMP and TbMP, and the short-term efficacy and safety results obtained with Creon CMP cannot be used to provide definitive evidence of the efficacy and safety of Creon TbMP. Thus, the efficacy and safety of Creon TbMP has not been demonstrated.

In order to resolve this deficiency, the Applicant will need to either demonstrate the efficacy and safety of Creon TbMP in at least one short-term efficacy and safety study (consistent with the Guidance for submission of PEP NDAs), or demonstrate clinical comparability of the two formulations. Given the inability of the Applicant to establish the comparability of the Creon CMP and TbMP with the bioactivity/bioequivalency (Bridging) study, the conduct of another bioactivity/bioequivalency study is not recommended, and any additional attempts to demonstrate the comparability of the two Creon formulations should only be done based on accepted clinical markers of effect, such as change in CFA.

In addition to the Clinical deficiency, there were several remaining CMC deficiencies noted by the CMC review team, including:

- Adequate control for (b) (4) activity in the measurement of lipase potency in release and stability testing of the Drug Substance and Drug Product.
- Adjustment of the acceptance criteria of (b) (4) used as lipase substrate for lipase potency measurements.
- Performance of dissolution testing of Drug Product on intact capsules.
- Definition of the acceptance criterion of the HPLC identity test used for Drug Substance and Drug Product.
- Drug Substance and Drug Product release test sampling plans need to be provided.
- Inconsistent lipase activity acceptance criteria for individual capsules need to be addressed.
- Information on the manufacturer and specifications of container, closure, and seals for Drug Substance packaging, and representative certificates of analysis for the seals used in the Drug Substance container/closure system need to be provided.
- The length of time that excursions in temperature are permitted for Creon capsules are to be specified in the Drug Product labeling.

These deficiencies are to be communicated to the Applicant in the Approvable letter.

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/s/

Anne Pariser
8/1/2007 04:37:19 PM
MEDICAL OFFICER

Daniel A. Shames
8/1/2007 04:50:13 PM
MEDICAL OFFICER

NDA:	20-725
Applicant:	Solvay Pharmaceuticals, Inc.,
Product:	Creon® (pancrelipase delayed-release) Capsules
Indication:	Treatment of pancreatic exocrine insufficiency (PEI)
Date Received:	May 11, 2007
Date Reviewed:	June 21, 2007
Reviewer:	Ethan D. Hausman, M.D., Medical Officer, DGP
Through:	Anne Pariser, M.D., Medical Team Leader, DGP

I. Introduction

The Sponsor, Solvay Pharmaceuticals, Inc., has submitted a new protocol for a clinical trial for the investigational use of Creon (pancrelipase delayed release) as a treatment for pancreatic exocrine insufficiency (PEI) under NDA 20-725. The protocol is intended to investigate Creon's use in treating PEI due to cystic fibrosis (CF). The Sponsor intends for the study to provide clinical experience with the Creon to-be-marketed product (TbMP; Creon® 24,000), for which the Sponsor seeks approval under NDA 20-725. Prior clinical trials were performed with Creon previously marketed or currently market products (CMP). To date, no clinical trials have been completed with the TbMP.

II. Background

Creon minimicrospheres (MMS) are derived from porcine pancreata and contain lipase, protease, and amylase. Pancreatic enzyme products (PEPs) have been marketed since before 1938, and are currently widely available without prescription as nutritional supplements. Per regulatory decisions posted in the Federal Register in the 1990s and in 2004, all PEPs must have an approved NDA after April 2008 in order to continue being marketed in the United States. An NDA was submitted for Creon in 1997 that received a Not Approved (NA) decision in 2003. A Complete Response to the NA was received November 20, 2006, and is currently under NDA review (NDA 20-725). The regulatory decision goal date for NDA 20-725 is August 17, 2007.

The Sponsor is also studying Creon TbMP under IND 47,546, wherein Creon TbMP's use will be investigated in patients with chronic pancreatitis (CP).

III. Review of Clinical Protocol

The Sponsor has submitted a clinical protocol titled: "A double-blind, randomized, multi-center, placebo-controlled, cross-over study to assess the efficacy and safety of Creon® 24,000 in subjects with pancreatic exocrine insufficiency due to cystic fibrosis." The proposed study is a randomized, double-blind (DB), placebo-controlled (PC), two-period cross-over, safety and efficacy trial comparing Creon MMS TbMP in 24 patients ($\geq$ 12 years) with PEI due to CF.

The Sponsor states that the primary objective of the study is "to demonstrate the superior efficacy of Creon 24,000 over placebo in improving fat digestion". The primary efficacy

variable will be change in the coefficient of fat absorption (CFA) assessed by the difference in CFA between placebo (CFA_0) and treatment (CFA_{Rx}) phases CFA (CFA_{Rx} minus CFA_0). Secondary efficacy objectives are assessments of coefficient of nitrogen absorption (CNA), stool fat, stool weight, and clinical symptoms (stool frequency, stool consistency, abdominal pain, and flatulence). Other secondary objectives include assessment of short-term safety parameters including vital signs, physical examinations, clinical laboratory analyses, and Adverse Events (AEs).

Patients will be eligible for study participation if they are male or female patients ages 12 years or older with a diagnosis of CF (by positive chloride sweat tests or gene analysis), have a diagnosis of PEI (by historical CFA <70% without supplementation, or current or historical human fecal elastase <50 μg/stool), are currently receiving treatment with a commercially available PEP and are on a stable dose of this PEP for more than three months, and are clinically stable (i.e., no evidence of acute respiratory disease or other acute condition). Patients will be excluded from study participation if they have evidence of ileus or acute abdomen, a history of fibrosing colonopathy, solid organ transplant, surgery affecting bowel or other notable underlying bowel disease, are using an immunosuppressive drug, are pregnant or lactating, or have known HIV infection.

The study will be divided into five study periods as follows:

1. Period 1: Visit 1 with screening, eligibility determination, and continuation of pre-study PEP therapy for one to seven days.
2. Period 2: Visit 2 with hospitalization and randomization into Creon TbMP or placebo group for five days of treatment. Stool collection for assessment of CFA will be collected over the terminal 72 hours of Period 2.
3. Period 3: All patients are discharged from the hospital and return to pre-study medication at pre-study dose for 10 to 14 days.
4. Period 4: Patients are again hospitalized. Patients who received Creon TbMP during Period 2 will receive placebo, and patients who received placebo during Period 2 will receive Creon TbMP. Stool collection for assessment of CFA will be collected over the terminal 72 hours of Period 4. Patients will be discharged from the hospital and from the study after completion of Period 4.

The study periods are represented schematically in the following figure (electronically copied and reproduced from the Applicant's submission):

Figure 1: Overall Study Design

Visit 1		Visit 2	**1st CO-Period**	Visit 3	Wash-out Period	Visit 4	**2nd CO-Period**	Visit 5
Day -7 to -1	1- 7 days	Day 1 of 1st CO-Period	5 days of study drug intake	Day 6 or 7 of 1st CO-Period*	10 to 14 days	Day 1 of 2nd CO-Period	5 days of study drug intake	Day 6 or 7 of 2nd CO-Period*
Screening	Subject's individual pancreatic enzyme treatment	**Randomization** to Creon 24,000/ placebo or placebo/Creon 24,000	**CFA** Stool collection** Dietary Diary Hospitalization on Day 1 of the 1st CO-Period	End of 1st CO-Period	Subject's individual pancreatic enzyme treatment		**CFA** Stool collection** Dietary Diary Hospitalization on Day 1 of 2nd CO-Period	End of 2nd CO- Period

The study visits and procedures are summarized in the following table (electronically copied and reproduced from the Applicant's submission):

Table 1: Study Visits and Procedures

	Visit 1 Screening[5]	**Visit 2 Randomization**	**Visit 3 End of 1st CO**	**Visit 4**	**Visit 5 End 2nd CO**
Day	-7 to -1	Day 1-1	Day 6 or 7-1[1]	Day 1-2	Day 6 or 7-2[1]
Informed consent	X				
Demographic data	X				
Medical history	X				
Inclusion/exclusion criteria	X				
Physical examination incl. height and weight	X		X	X	X
Vital signs	X	X	X	X	X
Laboratory safety tests	X		X		X
Pregnancy test[2]	X				
Clinical symptomatology	X	X	X	X	X
Clinical Global Impression	X	X	X	X	X
Concomitant medication	X		X		X
Adverse events	X		X		X
Dispense medication		X		X	
Collect medication			X		X
Compliance check			X		X
Hospitalization[4]		X		X	
Stool collection/dietary diary[3]			X		X

1- Day 6 or 7 depending on the appearance of the 2nd dyed stool
2- only if child-bearing potential
3- 1st stool marker has to be taken on the evening of Day2-1 and 2-2; the 2nd stool marker on the evening of Day 5-1 and 5-2, record on dietary intake in parallel
4- hospitalization from Day 1-1 to Day 6 or 7-1 and from Day 1-2 to Day 6 or 7-2

Day 1-1 Day 1 of 1st CO-Period
Day 6 or 7-1 Day 6 or 7 of 1st CO-Period
Day 1-2 Day 1 of 2nd CO-Period
Day 6 or 7-2 Day 6 or 7 of 2nd CO-Period

IV. Recommendations

The study is a randomized, double-blind, placebo-controlled, two-period cross-over, short-term safety and efficacy study of Creon MMS TbMP to investigate the primary efficacy (by CFA during treatment with Creon compared to placebo treatment) and short-term safety in patients with PEI due to CF, aged 12 years and older.

Demonstration of short-term efficacy with the TbMP is necessary as the Complete Response (CR) to the NA decision for the Creon NDA (currently under review) is likely to receive an Approvable decision, as the Applicant was not able to bridge the CMP with the TbMP with a bioavailability study. Since no clinical efficacy studies have been completed to date with the TbMP, at least one efficacy study will need to be performed with the TbMP to support the NDA submission for Creon (per the Guidance for PEI drug products). Therefore, constructive feedback to the Sponsor on study design for the proposed study, intended to optimize the study design in support of the NDA of the Creon TbMP, is warranted.

In the opinion of this Reviewer, the proposed study is safe to proceed as summarized in the clinical protocol; however, some protocol modifications are recommended for clarity (see comments to be communicated to the Applicant below).

V. Comments to be Communicated to the Applicant

The following comments are to be communicated to the Applicant:

"We refer to your May 11, 2007 submission of a new clinical protocol. The protocol (S245.3.126) is entitled, "A double-blind, randomized, multi-center, placebo-controlled, cross-over study to assess the efficacy and safety of Creon® 24,000 in subjects with pancreatic exocrine insufficiency due to cystic fibrosis."

We have completed our review of your submission, and have the following comments and recommendations.

1. Your inclusion criteria state that patients will be included in the study if they have "an historical Coefficient of Fat Absorption (CFA) <70% without supplementation or current or historical human fecal elastase < 50 μg/stool". State the time frame within which the screening CFA or fecal elastase must have been obtained in order to qualify the patient for entry into the study (e.g., within the last 12 months). Alternatively, incorporate a pre-study non-treatment phase wherein baseline CFA is assessed. Please also correct the elastase reference units to μg/g of stool.

2. The primary efficacy population should be the ITT population, that is, all subjects who were randomized and had taken at least one dose of study medication.

3. Propose how missing data will be accounted for in the analysis.

4. Clearly define the primary endpoint for the study. For example, if you intend to use the mean change of Creon treatment period CFA minus placebo period CFA as the primary endpoint, define this endpoint in your study protocol.

5. Please ensure that your study is adequately powered to demonstrate a clinically meaningful difference in CFA between the Creon and placebo treatment periods.

A clinically meaningful change in CFA has been described in the medical literature as a 30% increase in CFA from no-treatment to active treatment in the most severely affected patients (patients with a no-treatment CFA of less than 40%).

6. Based on your responses to items 2, 3, 4, and 5 above, please re-calculate sample size.

7. The doses indicated in sections 2 and 7.6 of your protocol indicate patients would be treated with the higher of either 4,000 lipase units/gram of fat intake per day or 2,500 lipase units/kg/meal. Please specify the dose you intend to study.

8. Clarify what is meant by the effect size of 0.7, as stated in section 10.8 on page 36 of the protocol.

9. Clearly define all other endpoints (e.g., secondary endpoints) in the study protocol.

10. Your final exclusion criterion states that patients will be excluded for known infection with HIV. Please clarify how HIV infection will be assessed.

11. Since FD&C Blue #2 dye will be administered to all patients as part of study procedures, include information about its adverse reaction profile in both the Investigator's Brochure and the patient Informed Consent form.

12. Section 7.8 (Prior and Concomitant Therapy) of your protocol states that "concomitant medications influencing and (sic) duodenal pH… and drugs acting on gastric emptying… or drugs interfering with bile secretion… can be given in a stable dose throughout the study". Please clarify how "stable dose" will be defined. For example, clarify over what period of time patients will have been taking the medication prior to study entry, state that the dose of the medication has not changed during this time, and state that the medication must be commercially available and be administered in the recommended dose range.

13. The Flowchart of Study Assessments (Table 2) is inadequate. Provide a flowchart that includes all study procedures to be performed by study day rather than grouped by phase as currently depicted in the study flowchart. For example, during Visit 2 Randomization, clearly delineate which protocol-defined treatments and procedures are to occur on each of the four to five days of this period.

14. In Section 8 (Study Assessments and Flow Chart) of the protocol, clearly list and describe in detail, all protocol-related procedures that are to be performed and recorded. For example, clarify on which days vital signs will be obtained and how often.

15. Ensure agreement between the study flowchart and the description of the study procedures in Section 8 (Study Assessments and Flow Chart).

16. No follow-up visit is scheduled after discharge from the inpatient unit at the end of the second cross-over period. Please add a follow-up visit (or telephone call) within several days after discharge for a safety assessment.

17. Define procedures to be used to verify compliance with all study-related procedures, such as compliance with study medications, concomitant medications, and patient self-collections of study endpoints (e.g., diary entries).

18. Your protocol does not state that assent will be obtained from patients ages 12 through 17 years. Per the Code of Federal Regulations (CFR), 21 CFR Part 50, Subpart D 50.52(c), any clinical investigation involving children should document that adequate provisions are made for soliciting the assent of the children. Please describe how you will obtain assent from patients ages 12 through 17 years participating in this study, and submit a copy of the model assent form to be used for our review.

19. Please submit sample Case Report Forms (CRFs), a model informed consent form, and a copy of the investigator's brochure with the revised protocol for our review.

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/s/

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6/22/2007 06:24:24 AM
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6/22/2007 07:46:07 AM
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Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products

Treatment of Steatorrhea in cystic fibrosis and chronic pancreatitis

NDA: 20-725

Sponsor: Solvay Pharmaceutical, Inc.

Drug: CREON® Minimicrospheres® (Pancrelipase Delayed-Release Capsules, USP)

Drug category: Exocrine pancreatic enzyme product, porcine-derived

Indication: Steatorrhea due to exocrine pancreatic insufficiency in cystic fibrosis and chronic pancreatitis patients

Date Document received by CDER: July 31, 1997 (Review suspended 9/24/97)
Review resumed April 9, 2003

Review status: Priority

PDUFA date: October 9, 2003

Date efficacy section assigned: May 30, 2003
Date safety section assigned: August 7, 2003
Date of Draft (efficacy and safety section): September 4, and September 15, 2003
Date review finalized: September 24, 2003

Medical Officer: Fathia Gibril, M.D., M.H.Sc.
Secondary Reviewer: Hugo Gallo-Torres, M.D., phD

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Clinical Review for NDA 20-725

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From clinical standpoint, the proposed drug is approvable for the indication of steatorrhea due to exocrine pancreatic insufficiency associated with cystic fibrosis and chronic pancreatitis. A final decision of approval will depend on the resolution of outstanding serious issues in chemistry.

B. Recommendation on Phase 4 Studies and/or Risk Management Step

There are no recommendations for phase 4 studies

II. Summary of Clinical Finding

A. Brief Overview of Clinical Program

In this application, Solvay has submitted NDA 20-725 and requested approval of Creon® Minimicrospheres® for the indication of steatorrhea due to pancreatic exocrine insufficiency (EPI) associated with cystic fibrosis (CF) and chronic pancreatitis (CP). In support of this request, the sponsor submitted data from three pivotal trials and two supportive studies.

Supportive studies (K245.5005 and K245.5002):

- With respect to the study K245.5005 in CP patients conducted in S. Africa, the sponsor indicated that the clinical conduct of the study was inadequate and that the verification of the source of documentation for the essential data elements generated in the study were doubted by the US and European Solvay compliance audit.

- The study K245.5002 in CF patients conducted in France was an uncontrolled, open-label trial comparing the test drug with Creon® Microshperes®. These data may add little if any to the two controlled CF studies submitted in this application. Further, from the regulatory point of view, equivalence to unapproved drug product would not add useful information.

Therefore, this review includes data from **three pivotal trials** to support the claim of safety and effectiveness of Creon® Minimicrospheres®, delayed-release capsules, for the treatment of steatorrhea due to EPI in CF and CP patients.

A total of 101 patients involving 74 CF patients and 27 CP patients were enrolled in these trials. The primary endpoint of these studies was to assess the effect of the test drug on steatorrhea as determined by coefficient of fat absorption (CFA).

- Two placebo-controlled, double-blind, multicenter, 2-arm, U.S. studies were conducted with Creon® 20 Minimicrospheres® capsules (20,000 lipase units, USP) in CF patients:

  (a) Study S2233101 was conducted in CF patients involving age 7 to 17 years (n=38).

  (b) Study S2233102 was conducted in CF patients involving age 18 to 53 years (n=36).

  The design of the two CF trials was identical. Both studies were randomized, double blind, parallel group, and multicenter studies with an open-label Creon® 20 run-in-phase for 2-3 weeks. The purpose of this phase was to ascertain an appropriate individualized stable dosing regimen and to determine a CFA from a 72-hour stool collection. Patients with a CFA > 80% were randomized to either Creon® 20 capsules or to placebo treatment during the double-blind phase. After a minimum of two days on double-blind treatment, a second 72-hour stool collection was performed. Patients were on high-fat (at least a 100 g fat/day) throughout the study period.

- One double-blind, randomized, placebo-controlled, 2-arm, multicenter U.S. study was conducted with Creon® 10 Minimicrospheres® capsules (10,000 lipase units, USP) in CP patients (223.2.01) involving age 38 to 74 years (n=27).

  The CP study consisted of two consecutive two-week outpatient treatment phases. Patients entered a 2-week, single-blind placebo run-in-phase in which eligibility for the second phase was established. Based on the 72-hour stool collection during the single-blind phase, patients who had a stool fat value ≥ 10 g/day and/or a CFA value of < 80% were eligible for double-blind randomization to either Creon® 10 or to placebo for two weeks. During both study phases, patients were instructed to take the study medications according to the following dosing regimen: 4 capsules/meal and 2 capsules/snack.

B. Background

Creon® Minimicrospheres® delayed-release capsule was introduced over 20 years ago as pancreatic enzyme replacement therapy for steatorrhea due EPI, mainly in CF and CP patients, the two most common causes of EPI. It is reported in the submission that the product has been marketed in over 50 countries worldwide including U.S. since 1987.

Pancreatic enzyme products (PEPs) were marketed prior to the Federal Food, Drug, and Cosmetic Act of 1938 and were generally recognized as safe and effective (GRAS and GRAE).

Because of the varying potencies of over-the-counter (OTC) and prescription enzyme preparations, the Agency issued a notice of proposed rulemaking in the Federal Register (FR) of July 15, 1991 that would establish that OTC PEPs are not generally recognized as safe and effective and are misbranded. Further, the Agency declared that it intends to consider all PEPs, whether currently marketed on a prescription or OTC basis, to be new drugs requiring an approved new drug application (NDA) for continued marketing.

The Agency published a final rule on April 25, 1995 concerning OTC PEPs. It was determined that all PEPs had to be marketed as prescription drug products and needed an approved NDA. The one approved PEP, Cotazym, immediate-release, on December 9, 1996, is not currently marketed. Currently there are no delayed-release PEPs that are approved in the US.

In compliance with FR notice, Solvay Pharmaceutical Inc. submitted an NDA 20-725 for a PEP, CREON® Minimicrospheres® (Pancrelipase Delayed-Release capsules) in July 31, 1997.

C Efficacy

In patients with EPI, a reduction in pancreatic enzyme output < 10% of normal is usually needed for maldigestion to occur. The major maldigestion problem arises from incomplete fat digestion; fewer problems arise from protein and carbohydrate malabsorption. Consequently, enzyme replacement is amid to improve or correct fat maldigestion.

Coefficient of fat absorption (CFA) assesses the effectiveness of lipase supplementation but not the effects of protease and amylase supplementation, hence, it is considered a surrogate endpoint. CFA is a well-established universally accepted marker for the assessment of efficacy of pancreatic enzyme replacement therapy. CFA (%) is calculated from fat ingested (g/24 hrs) and fecal fat excretion (g/24 hrs) ([Fat intake –Fat excretion/ Fat intake] x 100).

It should be noted that one cannot claim a specific CFA value that would satisfactorily assess treatment response in all patients. In other words, to claim a satisfactory response of a given therapy based on assessment of CFA, it is critical to demonstrate a significant change from baseline value rather than an absolute value on therapy.

Pancreatic enzyme dosing in cystic fibrosis is determined by individual body weight and age consistent with the Cystic Fibrosis Foundation Consensus Conference recommendation. Dosing in non-CF exocrine pancreatic insufficiency disorders is individualized and determined by the degree of maldigestion and malabsorption, the fat content of the diet and the lipase activity of each preparation.

The sponsor, Solvay pharmaceutical, Inc., submitted results from three randomized, multicenter, double-blind, placebo controlled, 2-arm, US clinical trials to support the use of Creon® Minimicrospheres® capsules for treatment of EPI in patients with CF and CP, in which the change in CFA from baseline to final assessment was the primary endpoint.
Baseline CFA values were determined from the 72-hour stool collection while patients were maintained on a high-fat diet and receiving either open-label Creon® 20 (CF studies) or a single-blind placebo (CP study). Final CFA values were determined from the 72-hour stool collection at the end of double-blind phase in each study.

The secondary efficacy endpoints were the change from baseline to final assessment in stool frequency, stool consistency and clinical global improvement (CGI) rated by a physician (CF studies) or clinical global impression of disease symptoms (CGIDs) rated independently by a physician and a patient (CP study).

Efficacy analysis result

(a) Cystic fibrosis study (S2233101)

Fourty-seven patients were enrolled in the Creon® 20 open-label phase for 2 to 3 weeks to ascertain an appropriate individualized dose regimen and to determine baseline CFA. Of these, 38 were qualified (CFA>80%) to continue in the double-blind phase: 19 were randomized to placebo treatment and 18 to Creon® 20 treatment for five to seven days (one patient withdrew from the study). The mean Creon® 20 dose taken during double-blind phase was 7855 lipase units/kg/day. The dose was established during open-label phase and was calculated for each patient as the mean number of capsules taken per day multiplied by the lipase content per capsule (20,000 units, USP) divided by body weight. Placebo patients received the number of capsules equivalent to the actual Creon capsules (Table 5 in this review).

Table A. Mean CFA values of the three trials (Reviewer's Table)

	Mean CFA (%)						
Protocol	**Open-label (OL) (Run-in phase) treatment***		Double-blind (DB) treatment		Change from OL to DB		p-value[#]
	Placebo N= 19	Creon 20 N= 18	Placebo N=19	Creon 20 N=18	Placebo N=19	Creon 20 N=18	
S2233101	86	87	52	84	-34	-3	<0.001
	N=18	N=18	N=18	N=18	N=18	N=18	
S2233102	88	89	51	87	-37	-2	<0.001
	Single-blind (SB) placebo phase		DB treatment phase		Change from SB to DB		
	Placebo N=14	Creon 10 N=12	Placebo N=14	Creon 10 N= 12	Placebo N=14	Creon 10 N= 12	
223.2.01	56	50	68	87	12	37	0.0185

*All patients received Creon® 20 capsules during open-label treatment; however, sample is broken down by double blind treatment assignment for comparison.
p-value is calculated based on analysis of variance method (ANOVA) with treatment as parameter. P-value was significant at 0.05 level.

The mean CFA values for each of the three pivotal studies are summarized in Table A.

The efficacy results from this study demonstrate statistically significant treatment differences between Creon®20 and placebo for the primary efficacy parameter (change from baseline CFA), and all secondary efficacy parameters (stool frequency, stool consistency, and CGI).

The difference between the two treatment groups in the change in mean CFA (primary endpoint) from open-label to double-blind treatment was highly significant ($p<0.001$). The mean CFAs of the placebo and Creon® 20 treatment groups were comparable after open-label Creon® 20 treatment (86% and 87%, respectively). After double-blind treatment, the mean CFA for the placebo group decreased by 34 percentage points to 52%; in contrast, the mean CFA for the Creon® 20 group decreased by only 3 percentage points to 84% ($p<0.001$).

As summarized in Table B, the sponsor analyzed results of fat intake and fecal fat excretion, the two parameters on which the CFA was based. There was no significant difference in fat intake between treatments in both phases ($p=0.46$). There was no apparent difference in fecal fat excretion between placebo and Creon® 20 groups during open-label treatment with Creon® 20 (16 .8 and 16.6 g/day, respectively). In contrast, there was significantly greater ($p=0.001$) increase in mean fecal fat excretion in the placebo group (62 g/day) compared with the Creon® 20 group (16.8 g/day).

For secondary efficacy endpoints, the change in the mean stool frequency from open-label to double-blind treatment decreased (-1.2) for patients randomized to Creon® 20 treatment and increased (4.3) for patients randomized to placebo treatment (P=0.002)

The most frequently reported stool consistency during open-label phase was "formed" (83% -89%) for both treatments. Similar percentage of patients (88%) reported "formed" stools following treatment with Creon® 20 during double-blind phase; in contrast, the majority of placebo treated patients (89%) reported "soft" stools and only 5% reported "formed" stools during double-blind phase. The change in consistency from open-label Creon® 20 treatment to double-blind treatment was significantly different between treatments (p=0.001). (Table 8 in this review).

The treatment differences were also significant for CGI scores rated by a physician (p<0.001). At the end of double-blind treatment, 89% of patients in Creon® 20 group were rated by a physician as either improved or remained unchanged as opposed to 32% of patients in placebo group (Table 17, vol. 20, page 1104).

b) Cystic fibrosis study (S2233102)

The design of this study was identical to the previous CF study. Fifty patients were enrolled in the Creon® 20 open-label phase for 2 to 3 weeks to ascertain an appropriate individualized dose regimen and to determine baseline CFA. Of these, 36 were qualified (CFA>80%) to double-blind phase: 18 were randomized to placebo treatment and 18 to Creon® 20 treatment for 6 to 8 days. The mean Creon® 20 dose received was 4537 lipase/units/kg/day for 6 to 8 days during double-blind treatment.

The efficacy results from this study demonstrate statistically significant treatment differences between Creon®20 and placebo for the primary efficacy parameter (change from baseline CFA), and all secondary efficacy parameters (stool frequency, stool consistency, and CGI).

The results in this study were similar to that of previous CF study in that the change in mean CFA from open-label to double-blind treatment was highly significant (p<0.001) (Table A). The mean CFAs for the placebo and Creon® 20 treatments were comparable during open-label Creon® 20 treatment (88% and 89%, respectively). After double-blind-treatment, the mean CFA for placebo group decreased by 37 percentage points to 51%; in contrast, the mean CFA for the Creon® 20 group decreased by only 2 percentage points to 87% (p<0.001).

Similar to the previous CF study, the amount of fat ingested was comparable between treatments (p=0.294); in contrast, fecal fat excretion was significantly

different between the treatments (p<0.001). There was no apparent difference in fecal fat excretion between the placebo and Creon® 20 treatment during open-label treatment with Creon® 20 (18.9 and 16.8 g/day, respectively). In contrast, there was significantly greater (p<0.001) increase in mean fecal fat excretion in placebo treatment compared with the Creon® 20 treatment (80 g/day vs 18 g/day, respectively).

The data for daily mean fat intake and fecal fat excretion for both CF studies are summarized in Table B.

Table B. Daily fat intake and fecal fat excretion (Reviewer's Table)

	S2233101		S2233102	
	Placebo (n=19)	Creon®20 (n=18)	Placebo (n=18)	Creon® 20 (n=18)
Daily fat intake (gram), mean ± SEM				
Open-label (OL) treatment*	139 ±1 2.76	128.3 ± 8.0	151.4 ± 8.2	151.2 ± 8.5
Double-blind (DB) treatment	131 ± 9.91	130 .2 ± 9.8	155.6 ± 8.7	145.7 ± 5.9
Change from OL to DB treatment	-7.7± 8.59	1.91± 4.98	4.2 ± 6.9	-5.5 ± 5.1
p-value#		0.459		0.294
Daily fat excretion (gram), mean ± SE M				
Open-label (OL) Treatment*	16.8±1.6	16.6±1.97	18.9 ± 2.3	16.8 ± 2.3
Double-blind (DB) treatment	62.19± 9.53	20.7±2.98	80.8 ± 13.6	19.1 ± 3.2
Change from OL to DB	45.37±8.41	4. 08±1.89	61.9 ± 11.8	2.3 ± 1.4
p-value#		0.001		<0.001

*All patients received Creon® 20 capsules during open-label treatment; however, sample is broken down by double blind treatment assignment for comparison
p-value is based on ANOVA with treatment as parameter, p-value was significant at 0.05 level.

Similar to the previous CF study, this study demonstrated significant treatment differences between Creon® 20 and placebo groups for all secondary efficacy parameters including stool frequency (p<0.001), stool consistency (p=0.001) (Table 14 of this review), and CGI scores (p<0.001) (Table 17, vol. 24, page 2995).

c) Chronic pancreatitis trial (protocol 223.2.01).

A total of 64 patients entered single-blind phase. Of these, 27 patients were qualified (stool fat ≥ 10 g/day and/or CFA <80%) to enter to a two-week double-blind phase: 13 were randomized to Creon® 10 capsules and 14 to placebo treatment. One patient was excluded from efficacy analysis due to missing data (lost stool collection). Therefore, 26 patients completed the study (14 placebo and 12 Creon® 10). The mean number of Creon® 10 capsules was 12.5 /day and the mean number of placebo capsules was 14.6 capsules during the double-blind treatment. The mean duration of exposure to the test drug was 15 days.

The efficacy results from this study demonstrate statistically significant treatment differences between Creon® 10 and placebo for the primary efficacy parameter

(change from baseline CFA), and secondary efficacy parameters (stool frequency, stool consistency) except for CGIDs scores.

As depicted in Table A, the difference between the two treatment groups in the change in mean CFA from the single-blind to the double-blind treatment was statistically significant (p=0.019). Mean CFAs at baseline for the placebo and Creon® 10 treatment groups were comparable during single-blind placebo-phase (56% and 50%, respectively). After double-blind treatment, the mean CFA for the placebo treatment increased by only 12 percentage points to 68; in contrast, the mean CFA for Creon® 10 treatment increased by 37 percentage points to 87 (p=0.019).

For secondary efficacy parameter, the change in mean stool frequency from single-blind placebo treatment to double-blind treatment was decreased (-5.6) for patients randomized to Creon® 10 treatment and was essentially unchanged (+0.6) for patients randomized to placebo treatment (p=0.0015). Similarly, there was a significant association detected between the change in stool consistency and treatments (p=0.010) in that during placebo treatment more "soft" stools were reported than during Creon® 10 treatment (Table 18 of this review).

There was no apparent difference in fecal fat excretion between placebo and Creon® 10 group during single-blind phase (63 g/day and 75 g/day, respectively). In contrast, there was significantly greater increase (p=0.018) in mean fecal fat excretion in the placebo treated group compared with the Creon® 10 treated group (75 g/day versus 18 g/day). (Table 17 of this review).
However, no significant differences between the two treatment groups were detected for CGIDs scores rated by the investigator (p=0.10) or by the patients (p=0.13), using Fisher Exact testes (Table 17 in this review).

Efficacy conclusion

The sponsor concluded that the data from three controlled studies consistently demonstrated that the Creon® Minimicrospheres® formulation is effective in the treatment of steatorrhea due to EPI associated with CF and CP.

Medical officer comment:
The efficacy results in three controlled trials achieved the goal stated in each protocol, i.e. treatment comparisons were considered statistically significant if $p \leq 5\%$.

The efficacy results from three pivotal studies demonstrated statistically significant treatment differences between Creon® Minimicrospheres® and placebo for the primary efficacy parameter (change from baseline CFA), and all secondary efficacy parameters (stool frequency, stool consistency, CGI in CF studies) except for CGIDs in CP patients.

The primary endpoint measure (change from baseline CFA) chosen by the sponsor is appropriate to assess the therapy response in patients with steatorrhea due to EPI. In these studies, the proposed drug product achieved a satisfactory response such that the mean CFA increased to 87% from the baseline CFA as low as 50%, which is perhaps the best one can get with most of currently available enzyme replacement therapies. It is worth mentioning that enzyme replacement therapies can hardly ever correct (normalize) fat maldigestion in the majority of patients, particularly in those with significant degree of malabsorption.

The data from the two CF trials demonstrated substantial evidence ($p<0.001$) to support the efficacy of Creon® 20 in ameliorating symptoms of steatorrhea. Further, the results demonstrated a considerable degree of reproducibility across both studies. Notable in these studies was that adult CF patients required a lower mean daily dose to ameliorate clinical symptomatology than did pediatric and adolescent CF patients (mean Creon® 20 dose 4537 lipase units/kg/day versus 7855 lipase units/kg/day, respectively). However, these CF studies did not involve children under age seven. Pancreatic enzymes are used in infants, toddlers, and preschool-age children with CF. The results from these CF studies may not be extrapolated to these age groups due to a considerable variation in the standard of care and mode of administration. Appropriate supporting data are required for these age groups.

Even though the efficacy results from Creon® 10 in CP study have achieved the stated goal, i.e. a statistically significant treatment comparison at 5% level of significance, the primary efficacy result may not be robust ($p=0.019$) for a single and small study to support the efficacy claim**.** However, in light of the robust and reproducible efficacy results shown across both CF trials, the efficacy claim in CP study could be adequately supported, given the close relation of the condition being treated, i.e. steatorrhea due to EPI in both study populations. Further, it is worth mentioning that CP is a rare condition with the estimated incidence rate about 5 per 100,000 inhabitants (orphan indication) and about 70% of the patients will develop EPI. Issues regarding one study approach are published in FDA "Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", US department of HHS, FDA, CDER, CBER, May 1998. Further, issues regarding studies in patients with EPI are published in FDA Draft "Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products-Submitting NDAs", US department of HHS, FDA, CDER, March 2003.

It should be noted that in reviewing the efficacy data presented in this application, this reviewer takes the following issues into account. The efficacy data is based on three randomized clinical studies with a short duration of exposure to the test drug, namely, four weeks in CF studies and two weeks in CP study. Since patients with EPI require life-long pancreatic enzyme replacement therapy, the quality assurance of the drug product becomes an important factor in addressing the long-term safety and efficacy of the test drug. Due to the inherent lability that has been historically observed with PEPs, a potential inconsistency in drug potency from Batch-to-Batch may exist. As a result,

patients may receive a lower or higher dose than intended, a possible efficacy and safety concern. Consequently, the clinical outcome from the three trials submitted may not be valid without adequate information in chemistry. The outstanding serious chemistry issues raised by Dr Martin Haber, chemistry reviewer, are the following:

1) The applicant has not provided drug substance characterization data.
2) Consistency with respect to chemical identity and biological activity has not been demonstrated.
3) The proposed specifications for drug substance (based on the USP monograph) are inadequate.
4) More appropriate specifications based on characterization data including tests for identity, biological activity, purity, impurities, and degradants are needed.
5) (b) (4)
6) The viral safety evaluation has not yet been completed.
7) The proposed storage is at room temperature, in which the drug substance is markedly unstable at the proposed room temperature.

C. Safety

The integrated safety database contains information from 33 clinical trails involving a total of 1179 patients. Of these, 677 had CF, 299 had CP, 94 had pancreatic surgery and 109 had diabetes. These studies were conducted worldwide between July 1985 and November 2000, including the three pivotal trials (2 for CF and 1 for CP) in this NDA submission.

A total of 924 patients received Creon® Microshperes® (Creon MS), 416 patients received Creon® Minimicrospheres® (Creon MMS), 369 received placebo and 311 received other pancreatic enzyme replacement therapy (PERT). (**Note:** Since the majority of studies were crossover designs, patients appearing in the total treatment group were counted several times). The predominant exposure within integrated studies was 2 to 4 weeks. No patient in the Creon MMS group and no patient in the placebo group was treated for more than 26 weeks. The most common daily median lipase dose taken in all treatment groups was in the range of 2,000 to 10,000 U/kg, i.e. 49% with Creon MS, 51% with Creon MMS and 51% with PERT.

The trials completion rate was high in all Creon studies (about 90%). The overall rate of discontinuations due to adverse evens (AEs) was very low and similar in the Creon MMS group (1.9%), in the Creon MS group (1.7%), and in the placebo group (1.6%). The two main AEs that led to withdrawal were body as a whole (1.4%) mainly due to abdominal pain, and the digestive system (1.4%) mainly due to diarrhea and nausea.

Serious advert events (SAEs) including one death were reported in 70 of 1179 patients (6%) (Table 8.8.6.2.1.1, Appendix 3 in this review). The most affected body systems were the body as a whole in 2.5%, respiratory system in 1.7%, digestive system in 1.1%,

metabolic and nutritional system as well as cardiovascular system in <1% of patients. The highest incidence rate of SAEs in the Creon group was observed in open, uncontrolled trails with 10% SAEs compared to half of the incidence in controlled trials. The incidence rate of SAEs in controlled trials was comparable among Creon, placebo and other PERT groups. The events reported were predominantly hospitalizations related to the underlying disease state and were considered as not related to the study medication. These complications consisted of conditions such as pneumonia, lung disorder, pancreatitis and abdominal pain. The one reported death was also related to underlying disease (Narrative under ISS section in this review).

Approximately 65% of all patients experienced at least one treatment emergent adverse event (TESS). The body systems most affected were the body as a whole (43%), digestive system (29%), respiratory system (23%), and metabolic as well as nutritional system (9%). The incidence rates were comparable in the Creon MS and Creon MMS patients (51% each), whereas the other PERT and placebo groups had slightly lower incidence (46% and 42%, respectively) (Table 8.8.8.1.1, Appendix 4 in this review).

Drug related hyperuricosuria was seen in 5/31 (16%) adult CF patients and 2/34 (5%) pediatric/adolescent CF patients. The increase in urinary uric acid excretion was most likely due to purine content of pancreatic extracts. This laboratory data was from two CF trials in this application and the results are from participants who completed both open-label and double-blind 24-hour urine collections (S2233101, 34 patients; S2233102, 31 patients).

Bases on the reported findings, this reviewer conclude that overall, the proposed drug showed an acceptable safety margin with its use in patients with steatorrhea due to EPI associated with CF or CP treated for two to four weeks in the majority of cases. However, since patients with these conditions require life-long enzyme replacement therapy, long-term safety of the study medication cannot be determined from data presented in these randomized clinical studies. The percussion section of the label should include information for physicians to use cautions in patients with gout or renal impairment due to hyperuricosuria associated with the drug product.
Note: Postmarketing experience has been addressed under appropriate section of this review.

D. Dosing

In the proposed package insert, in the Dosage and Administration section the sponsor proposes the following:
(1) Pancreatic enzyme dosing in cystic fibrosis:

Pancreatic enzyme dosing in cystic fibrosis is to be determined by individual body weight and age consistent with the Cystic Fibrosis Foundation Consensus Conference recommendation (Borowitz et al, The J of Pediatrics November 1995):

- Dose begins with 1000 USP lipase units/kg/meal for children < four years of age, and 500 USP lipase units/kg/meal for > fours years of age.
- Dosage to be adjusted according to the severity of the disease, control steatorrhea and maintenance of good nutritional status.
- Doses in excess of 2500 USP lipase units/kg/meal should be used with caution and only if they are documented by three-day fecal fat measurements to significantly improve the coefficient of fat absorption.
- Doses in excess of 6000 USP lipase units/kg/meal have been associated with fibrosing colonopathy.

(b) (4)

Reviewer's comment:
The two pivotal studies in CF did not involve children under age seven. Pancreatic enzymes are used in infants, toddlers, and pre-schooled-age children with CF and the proposed labeling includes these age groups. Appropriate supporting data are required for these age groups.

E. Special Populations

Assessment of the use of test drug may not provide meaningful information in special populations in these randomized trials. There were very few patients in CP trial that were older than age 65 and very few patients in CF trials who were younger than age 12.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Creon® Minimicrospheres® capsules are orally administered and contain delayed-release Minimicrospheres of porcine-derived Pancrelipase. The pancreatic enzymes (lipase, protease and amylase) 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 pancreatic enzymes in Creon® Minimicrospheres® capsules are enteric-coated to resist gastric destruction or inactivation. The Minimicrospheres® formulation includes Creon® 5, 10 and 20 capsules, which are identical to each other in formulation but vary only in quantity of Minimicrospheres® used to create the different enzyme strength. Minimicrospheres® are sized to produce homogenous mixing with chyme as it is released into the duodenum. Once in the duodenum, the enteric coating dissolves in response to the increased pH (≥ 5.5)

Name of Drug
Generic name: Pancrelipase (Delayed-Release Capsules, USP), porcine.
Proprietary name: CREON® Minimicrospheres® capsules
Category: Exocrine pancreatic enzyme drug product

Proposed label for drug product in the NDA 20-725 is as follow:

(b) (4)

(b) (4)

B. State of Armamentarium for Indication(s)

- Pancreatic enzyme preparations (PEPs) of porcine or bovine origin have been available in the U.S. as prescription and over-the-counter (OTC) products for the treatment of exocrine pancreatic insufficiency (EPI) in children and adults

with cystic fibrosis (CF) and in adults with chronic pancreatitis since before the enactment of the Federal Food, Drug, and Cosmetic Act of 1938.

- On November 18, 1978, the Advisory Review Panel on OTC Miscellaneous Internal Drug Products recommended that all PEPs be available on an OTC basis only. Based on this recommendation, the Agency published an initial monograph on PEPs in the Federal Register of December 21, 1979 and a tentative final monograph on November 8, 1985.

- Due to comments received from the Cystic Fibrosis Foundation, health care professionals and drug manufacturers, the Agency reversed the initial ruling of PEPs as safe and effective (GRAS and GRAE). The Federal Register (FR) of July 15, 1991 established that OTC PEPs are not GRAS and GRAE.

- In FR of April 25, 1995, the Agency declared that all PEPS, whether currently marketed on a prescription or an OTC basis, to be new drugs that require a new drug application (NDA) for continuing marketing. The only one approved PEP (Cotazym, immediate-release) on December 9, 1996 is not currently marketed.

- The Agency has also determined that PEPs are medically necessary and accordingly, is allowing manufacturers to continue marketing and obtain approval of their products within four years (2007). Currently there are a number of different PEP formulations available for patients with EPI.

A list of various marketed pancreatic enzyme products is shown in the Table below (scanned from Division file).

Name	Manufacturer	Lipase (USP)	Protease (USP)	Amylase (USP)	P/L	A/L	Dosage form
Pancreatin 8X USP 900mg. (high lipase)	Vitaline	22,500	180,000	180,000	8.00	8.00	Uncoated tablets
Pancrease	McNeil	4,000	25,000	20,000	6.25	5.00	enteric coated microspheres
Pancrease MT4 (*Panzytrat*)	McNeil (*Knoll*)	4,000	12,000	12,000	3.00	3.00	"
Pancrease MT10 (*Panzytrat*)	"	10,000	30,000	30,000	3.00	3.00	"
Pancrease MT16 (*Panzytrat*)	"	16,000	48,000	48,000	3.00	3.00	"
Pancrease MT25 (*Panzytrat*)	"	25,000	75,000	75,000	3.00	3.00	"
Creon 25 (Pancreatin) (USP)	Solvay	25,000	62,500	74,700	2.50	2.99	"
Creon 25 (Pancreatin) (BP)		25,000	467*	18,000*			"
Creon (Pancreatin,Amylase)	Solvay	8,000	13,000	30,000	1.63	3.75	"
Donnazyme (Pancreatin)	Robins	1,000	12,500	12,500	12.5	12.5	Tablets
Entozyme (Pancreatin)	Robins	600	7,500	7,500	12.5	12.5	Tablets
Cotazym (Pancrelipase)	Organon	8,000	30,000	30,000	3.75	3.75	Powder in gelatin capsule
Ku-Zyme HP (Pancrelipase)	Schwarz Pharma	8,000	30,000	30,000	3.75	3.75	Powder in gelatin capsule
Ultrase MT6	Scandipharm	6,000	19,500	19,500	3.25	3.25	enteric coated spheres
Ultrase MT12	"	12,000	38,000	19,500	3.17	1.63	"
Ultrase MT18 (*Pancrease HL*)	Scandipharm (*Cilag*)	18,000	58,500	58,500	3.25	3.25	"
Ultrase MT20 (*Pancrease HL*)	"	20,000	65,000	65,000	3.25	3.25	"
Ultrase MT24 (*Pancrease HL*)	"	24,000	78,000	78,000	3.25	3.25	"
Ultrase MT30 (*Pancrease HL*)	"	30,000	97,500	97,500	3.25	3.25	"
Viokase	Robins	8,000	30,000	30,000	3.75	3.75	Tablet (no size)
Viokase	"	16,800	70,000	70,000	4.17	4.17	Free Powder (700 mg)
Zymase Capsules (Pancrelipase)	Organon	12,000	24,000	24,000	2.00	2.00	enteric coated spheres
Nutrizym (BP Units)	E.Merck	10,000	560	10,000			

C. Important Milestones in Product Development

Drug product history (Obtained from Division file)

At the pre-NDA meeting Solvay provided the following information on the drug product:

- In 1926 the Creon brand of pancreatic enzyme was first introduced in Germany
- In 1982 Creon capsules with 8000 USP units of lipase, delayed-release capsules containing enteric-coated Minimicrospheres, was introduced in Germany
- In 1987 Creon 8000 USP was introduced for commercial distribution in the U.S. This drug product is currently registered for marketing in over 50 countries worldwide under various trade names

- In 1992 Creon 25 capsules, containing 25,000 USP units of lipase, was introduced in the U.S and voluntarily withdrawn in 1994 due to reports of colonic stricture in pediatric cystic fibrosis (CF) patients on enzyme replacement therapy with high lipase activity (>20,000 USP units) delayed-release pancreatic enzyme drug products.
- In 1993 Creon 8 capsules was discontinued in the U.S and replaced with Creon 10 capsules, containing 10,000 USP units of lipase.

D. Other Relevant Information

On September 10, 1991, FDA published the "Application Integrity Policy" in the Federal (56 FR 46191); "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities). For Firms that are impacted by the policy, FDA generally defers substantive scientific review of data in pending applications or supplements while a validity assessment is completed by the Agency to determine the reliability of the submission.

Solvay Pharmaceutical, Inc (SPI) originally submitted NDA 20-725 in July 31, 1997. However, in September 24, 1997 the Center for Drug Evaluation and Research suspended substantive scientific review of all applications involving SPI in Marietta, GA and Baudette, MN since both facilities were impacted by the policy outlined above. On April 9, 2003 FDA has resumed substantive review of the application after SPI prepared and implemented a Corrective Operation Plan, which appeared to provide sufficient safeguards to preclude future wrongful acts and non-compliance with regulatory requirements.

E. Important Issues with Pharmacologically Related Agent

None

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There are major chemistry issues that are clinically relevant. This reviewer shares the concern raised by Dr Martin Haber, chemistry reviewer, and should be adequately addressed by the sponsor. The deficiencies are as follow:
The drug substance is an extremely crude natural product material, derived from hog pancreas.

1) Drug substance characterization was never done by the applicant,
2) Drug substance reference standards are inadequate,

3) Drug substance specification is inadequate and requires specific tests for identity and purity,
4) Drug substance stability is poor,
5) Drug product specifications are inadequate and requires specific tests,
6) Drug product stability cannot be evaluated until tests are established
7) The drug substance is markedly unstable at room temperature and proposed storage is at room temperature,
8) Drug substance viral safety evaluation is not completed.

The statistical methods were adequately addressed in submitted studies. There was no major safety concern with respect to pharmacology-toxicology review according to Dr Jasti Choudary, pharm-tox supervisor. According to Dr Suliman Al-Fayoumi, biopharm reviewer, the sponsor's proposed dissolution test method is acceptable provided that the sponsor adequately addresses the following issues:

- The acid stage should be modified to last for 2 hrs instead of (b) (4)
- An acceptance limit should be set for the acid stage.

With regard to data from $^{13}CO_2$-hiolein breath test the biopharm reviewer has listed some shortcomings to be forwarded to the sponsor.
The reader may refer to the individual reviews for detail information.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Pancreatic enzymes are intended to act directly in the gastrointestinal tract, therefore, bioavailability studies are not useful.

B. Pharmacodynamics

NA

IV. Description of Clinical Data and Sources

A. Overall Data

The sponsor submitted results of three pivotal trials and two supportive trials in support of the claim of safety and efficacy of Creon® Minimicrospheres® capsules for the indication of steatorrhea due to EPI associated with CF and CP patients.

Supportive trials ((K 245.5005 and K245.5002):
For the study K 245.5005 on chronic pancreatitis patients conducted in S.Africa, the sponsor indicated that the clinical conduct of the study was inadequate and

that the verification of the source of documentation for the essential data elements generated in the study were doubted by the US and European Solvay compliance audit. The K 245.5002 study on CF patients conducted in France was uncontrolled trial comparing Minimicrospheres with Microshperes. These data may add little if any to the two controlled CF studies submitted in this application. Further, equivalence to unapproved drug product would not help from regulatory point of view.

The reviewer therefore, will focus on the data supporting the claim of safety and efficacy of Creon® Minimicrospheres® capsules from **three pivotal trials** conducted by Solvay Pharmaceutical, Inc. for two indications:

1. Two trails for the indication of steatorrhea due to EPI associated with CF patients:
   - S2233101 in pediatric and adolescence CF patients.
   - S2233102 in adult CF patients.
2. One trial for the indication of steatorrhea due to EPI associated with CP patients (223.2.01).

B. Tables Listing the Clinical Trials

Tables 1 and 2 (scanned from amendment submitted on July 1, 2003) list three pivotal and two supportive studies, respectively.

The three pivotal studies including study design, treatment duration, age and gender of patients are listed in Table 1.

In these pivotal trials, a total of 101 patients were studied. Of these 38 were pediatric/adolescent CF patients (S2233101), 36 were adult CF patients (S2233102) and 27 were CP patients (223.2.01). The mean age was 12 years for pediatric/adolescent CF patients, 23 years for adult CF patients and 51 years for CP patients.

The two supportive studies (K245.5005 and K245.5002) are listed in Table 2.

TABLE 1
Completed and Reported Pivotal Well Controlled Studies
CREON® MINIMICROSPHERES®
(Pancrelipase Delayed-Release Capsules, USP)

Study No. & Site/Location in NDA	Subject Population	Design	Blinding	Control Type	Reference Product	Treatment Duration	Creon declared lipase units	Age Range (mean)[1]	Sex[1]	Dose caps/day	N[2] Creon	N[2] Placebo
S223101 USA/ NDA vol. 20 pg. 1029	Cystic Fibrosis	Parallel	Double-Blind	Placebo	-	4 weeks	20,000 USP	7-17 (12.5)	18 M 20 F	13.3 (mean)	18	20
S223102 USA/ NDA vol. 24 pg. 2908	Cystic Fibrosis	Parallel	Double-Blind	Placebo	-	4 weeks	20,000 USP	18-53 (23.8)	22 M 14 F	12.5 (mean)	18	18
223.2.01 USA/ NDA vol. 30 pg. 5203	Chronic Pancreatitis	Parallel	Double-Blind	Placebo	-	2 weeks	10,000 USP	31-74 (51.4)	18 M 9 F	12.5 (mean)	13	14

[1]Safety sample
[2]Total treatment group numbers retrieved from clinical reports/publications and representing populations after randomization

TABLE 2
Completed and Reported Supportive Studies
CREON® MINIMICROSPHERES®
(Pancrelipase Delayed-Release Capsules, USP)

Study No. & Site/Location in NDA	Subject Population	Design	Blinding	Control Type	Reference Product	Treatment Duration	Creon declared lipase units	Age Range (mean)[1]	Sex[1]	Dose caps/day	N[2] Creon	N[2] Placebo	N[2] active Reference Product
K.245.5005 S. Africa/ NDA vol. 33 pg. 6455	Chronic Pancreatitis	Parallel	Double-Blind	Placebo	-	3 weeks	10,000 Ph. Eur.	39-68 (53.4)	31 M 2 F	16	17	16	-
K.245.5002 France/ NDA vol. 35 pg. 7496	Cystic Fibrosis	Crossover	Open-Label	Active	Creon 12,000	4 weeks	10,000 USP	3-25	41 M 28 F	9.3 (mean)	69	-	69

[1]Safety sample
[2]Total treatment group numbers retrieved from clinical reports/publications and representing populations after randomization

C. Postmarketing Experience

Creon capsules are registered for marketing in over 50 countries worldwide and are available in both the Microshperes and Minimicrospheres formulations. The sponsor stated that none of these products has been withdrawn from the foreign market due to safety concerns. The sponsor indicated that postmarketing adverse event reports were selected from the sponsor's database, spontaneous reporting, literature, authorities and FDA MedWatch Medical Product Reporting Program. The events were grouped by body system using COSTART terminology. The adverse events from clinical studies are reported under integrated safety summary (ISS).

Note: During the original NDA submission in July 1997, the sponsor provided postmarketing experience reports between October 21, 1982 and March 15, 1997. In December 2001, the sponsor provided additional postmarketing experience reports covering between March 16, 1997 and September 30, 2001. The sponsor stated that a crude estimate of the number of patients exposed to pancreatin during the period of March 16, 1997 to September 30, 2001 was estimated from worldwide sales volume. It has been assumed that each patient received an average dose of 2.2 g pancreatin daily and has continued treatment for an average of 365 days.

The reviewer will combine the reports from both submissions as deemed appropriate.

Postmarketing adverse events (AEs) summary

This section summarizes AEs reported between March 16, 1997 and September 30, 2001 since the sponsor indicated that overall, the conclusion reached in the original submission of July 1997 remained unchanged.

It has been estimated that patient exposure to pancreatin during the period of the safety update was more than 800,000 patient-years. In this safety update, the database contains a total of 298 postmarket adverse events (AEs) experienced with varying strength and formulations of Creon by 231 foreign and domestic patients.

The most commonly reported AEs (≥ 5 reports) encompass the digestive, body as a whole, skin and appendages. The gastrointestinal events of abdominal pain (32) diarrhea (27), flatulence (14), constipation (8), malabsorption syndrome (8), nausea (7), and vomiting (6) are comparable in quality and frequency with the figures given in the original submission. Integumentary events of rash (6), urticaria (7) and pruritus (9), lack of drug effect (4) have decreased slightly as compared to that reported in 1997 submission. Product quality could not be determined to be the cause of any of these events.

Serious Adverse Events (SAEs) summary
Intestinal stenosis, intestinal obstruction, stenosis of colon and colitis were event categories, which yielded the greatest number of SAE reports. These cases will be addressed together with fibrosing colonopathy.

Four deaths were reported including one death (first case) reported in 1997 submission:

- The first case was (PANC003970007) a 14 year-old female with severe pulmonary disease, who died 9 months into a study investigating the relative contribution of optimal nutritional support in cystic fibrosis. Children in this independent study were given enteric-coated Creon Microshperes in an individualized dosage, and were instructed to take a high-fat diet. A telephone call to the author of this report revealed that the death was not related to the drug product, but rather to the child's underlying pulmonary condition.

- The second case an 86-year-old male with a history of mitral regurgitation and cardiomyopathy was hospitalized for aggravated cardiac insufficiency while he was treated with a total of five suspected drugs (pancreatin, fluvoxamine, tinaptine, acetysalicilate lysine and digoxine). All drugs were regarded as having a remote or unlikely causal relationship to the occurrence of the adverse events. The patient died 19 days after the onset of the reaction. No further information is available (PANC01888980002).

- The third case occurred in a 70-year-old patient (unknown sex) with a history of neuropathy. After 2.5 years treatment with Creon for chronic pancreatitis and an overall good condition, the patient was hospitalized for treatment of anemia and received blood transfusion. After 2 days in hospital the patient fell, suffered subarachnoidal hemorrhage and died 12 days later. The reporter assessed the causal relationship as unrelated to Creon (PANC00399001346).

- The fourth case was a 70 year-old female with a history of adenocarcinoma. She experienced anemia and thrombocythopenia while she was being treated with five suspect drugs (Creon, omeprazole, prednisone, bromazepam, and gemcitabine) the adverse events occurred on an unspecified date. The platelet has decreased to 12000/ul but then started to improve. All drugs were stopped, the patient died on an unknown date. Death was not linked to the reported AEs. All drugs were regarded as having an unlikely causal relationship to the occurrence of the AEs (PANC00301001069).

  The sponsor concluded that overall, there were few serious adverse event reports in the postmarket experience relative to the volume of drug used worldwide. Creon therapy can be regarded as safe in treatment of exocrine pancreatic insufficiency associated with cystic fibrosis and chronic pancreatitis.

Fibrosing colonopathy (FC), intestinal obstruction and colitis

Note: The first section of this summary includes reports from July 1997 submission followed by reports from September 2001 submission.

Using the COSTART dictionary for the occurrence of events that might be related to fibrosing colonopathy, the sponsor identified 37 cases/reports in the postmarketing report submitted in 1997:

- In all 37 cases pancreatic enzyme therapy was used. Seven cases were excluded from further evaluation, since in four cases Creon use was excluded and in three cases Creon use was not confirmed.

- In 17 of the remaining 30 cases, a highly probable cause of symptoms other than fibrosing colonopathy was identified.

- In 11 of 17 cases, the probable diagnosis was distal intestinal obstruction syndrome (DIOS). Of these, 11 three were confirmed by histology, and 8 have responded to conservative measures.

In the remaining 6 of 17 cases, diagnoses other than fibrosing colonopathy or DIOS were probable:

- Case PANC002940013 was a 64-year-old male with duodenal narrowing probably related to prior peptic ulcer disease.
- Case PANC00394007 was a 59-year-old male with history of acute pancreatitis. He presented with a stricture of the left side of the transverse colon and perforation of the cecum. The stricture was thought to be due to colonic ischemia occurring during episode of acute pancreatitis.
- Case PANC003940016 was an 88 year old female with severe constipation which was relieved by water and laxative enema.
- Case PANC003940018 was a 25-month-old female with CF who was asymptomatic. A routine ultrasound (US) showed two areas of bowel wall thickening in the small intestine. Small bowel intussusception was considered as a possible diagnosis. A repeat US showed that the lesion had reduced in size. The patient remained asymptomatic.
- Case PANC00395001 was a male in his mid-50s with pancreas divisum. He presented with worsening abdominal pain in 1994 and was found to have fibrotic stricture in the terminal ileum and jejunum.
- Case PANC003950012 was a 5-year-old female with CF who presented with recurrent abdominal pain. At surgery, a pericolic abscess and obstruction due to viscid mucus admixed with inflammatory polyps in a region of colonic inflammation were found.

In the remainig13 of the 30 cases, the sponsor reported that there was histological evidence suggestive of **fibrosing colonopathy.** These cases are listed in Table 8.6.2.3.5.4.2 (scanned, vol. 57, page 16088). The sponsor indicated that all of these cases had received other pancreatic supplements in addition to Creon.

The main products used in the 12 months prior to surgery for fibrosing colonopathy were Eurobiol® 25000, Nutrizym® 22, Pancrease® HL, Pancrease® MT 25 and Ultrase® MT 24.

The sponsor stated that exposure to Creon products was limited in these cases. Five cases received Creon products in the period from 24 to 12 months before surgery for fibrosing colonopathy and then switched to non-Creon products; five cases received Creon 25000 in the period from 12 to 7 months before surgery and then switched to non-Creon products.
The remaining three cases switched from Ultrase® MT 24, Pancrease MT 25 and Pancrease HL, respectively, to Creon products shortly before surgery as follows:

- Case PANC002940011 received Ultrase® MT 24 for about 15 months until March 1994. She switched to Creon 10 for 3 weeks and then to Pancreas for 6 weeks. During the 3 weeks on Creon® 10, severe constipation was diagnosed. She underwent surgery for fibrosing colonopathy in March 1994.
- Case PANC002940014 was treated with Pancrease® MT 25 for 9 months presented with a 7-month history of rectal bleeding. She switched to Creon® 25 for 10 days when she underwent surgery for fibrosing colonopathy.
- Case PANC003940004 was treated with Pancrease® HL for about 12 months. He devolved bloody diarrhea and was then switched to Creon 25 for one month and then to Creon for three months before surgery for fibrosing colonopathy.

The sponsor concluded that there was no case of fibrosing colonopathy confirmed by histology in which Creon was taken alone. With the exception of three cases, no child was treated with Creon in the seven month before surgery. Two of the children who were exposed to Creon shortly before surgery had already developed symptoms of fibrosing colonopathy on non-Creon product. The third child received Creon for only 21 days.

TABLE 8.6.2.3.5.4.2.
Concomitant Enzyme Supplement Drugs listed in Reports of suspected Cases of Fibrosing Colonopathy

PRODUCT(S)	MANUFACTURER REPORT NUMBER (DER)
CREON® 8000 + CREON® 25000 + Pancrease® HL	PANC000930001
CREON® 8000 + CREON® 25000 + Pancrease® HL	PANC000930002
Unknown enzyme + CREON® 25000 + Eurobiol® 25000	PANC000930005
Unknown enzyme + CREON® 25000 + Pancrease® HL	PANC000930006
CREON® + CREON® 25000 + Pancrex® V + Pancrease® HL + Nutrizym® 22	PANC003930003
CREON® 25000 + Pancrease® HL + Nutrizym® 22	PANC000940007
CREON® 25000 + Pancrease® HL	PANC000940009
CREON® + Nutrizym® 22	PANC000940010
CREON® 25000 + Pancrease® + Pancrease® HL	PANC000940012
CREON® 25000 + Pancrease® + Pancrease® HL	PANC000940014
CREON® 10 + Pancrease® + Ultrase® 24 + Viokase	PANC002940011
CREON® 25 + Pancrease® MT 16 + Pancrease® MT 25	PANC002940014
CREON® 8000 + CREON® 25000 + Pancrease® + Pancrease® HL	PANC003940004
Unknown enzyme + Pancrease® HL	PANC000930007*
Unknown enzyme + Pancrease® HL	PANC000940008*
Unknown enzyme + Nutrizym® 22	PANC000930003*
Pancrease® MT + Ultrase® MT 24	PANC000930008*
Pancrease® MT + Ultrase® MT 24	PANC000930009*
Pancrease® MT 4 + Pancrease® MT 16 + Pancrease® MT 25	PANC000940001*
Pancrease® MT 25 + Ultrase® MT 24	PANC000950001*

* Cases in which Creon treatment could be excluded or the enzyme product was not referenced.

Since March 1997 submission, **fibrosing colonopathy** has been reported in the following three adults in the literature. In two cases Creon is not involved, and in the other case Creon had been discontinued seven years before diagnosis of FC:

- A female with CF and chronic DIOS received no regular pancreatic enzyme supplementation until 1994 when at age 23, she began treatment with Panzytral® 25,000 with maximum dose of 17,000 lipase units/kg/day. Four months later her abdominal complaints worsened. Laparotomies for mechanical ileus and adhesions were performed 3 times. She underwent another laparotomy for recurrence of ileus where distal small bowel and ascending colon were resected. Colonic histology was consistent with fibrosing colonopathy (Hausler et al, 1998).

- In her late 40s, a non-cystic fibrosis female with gallstone disease suffered an episode of acute pancreatitis following shpincterotomy. She continued to have pain and was commenced on treatment with Creon in 1988. In 1990 Creon was changed to Pancrease®, 3000 lipase units/kg/day. She underwent pancreaticoduodenectomy for persistent pain. In 1991 treatment was changed to Nutrizym GR (17,700 lipase units/kg/day) and

then to Nutrizym® 22 38,000 lipase units/kg/day. In 1995 a diagnosis of Crohn's disease of the ascending colon was made. Subsequently, she began mesalazine 400 mg tid and continued treatment with Nutrizym. In 1997 a right hemicolectomy was performed and histology confirmed fibrosing colonopathy (Bansi et al, 2000).

- A 56-year-old woman presented in 1988 with constipation and bleeding per rectum. Colon biopsy confirmed Crohn's disease. She was treated with Eudragit-coated mesalazine 800 mg tid. One year later she developed stenosis of the right colon, which was resected at surgery. Histology confirmed fibrosing colonopathy (Gaia et al, 2001).

The sponsor made a comment that the first two cases were exposed to Eudragit L30D55-coated pancreatic enzymes. The second case additionally received mesalazine, a tablet formulation coated with Eudragit L30D55. The third case only received Eudragit-containing mesalazine. The sponsor stated that **Creon dose not contain Eudragit.**

The following four suspected cases of **FC**, three with histological confirmation, had received Creon products in addition to other pancreatic enzyme brands.

- After the use of unknown brand for an unknown period of time an 8-year-old boy with CF presented with chronic diarrhea and cramps. One year later he developed bloody diarrhea. Biopsy with colonoscopy revealed non-specific acute inflammatory infiltrate. One year later he underwent right colectomy for a tight stricture in the cecum that was consistent with FC. He had another surgery for recurrence of FC. One year later, persistent narrowing of the remaining colon segment was found (Moss et al: PANC00399000418)

- A three-year-old cystic fibrosis male was treated with Creon® 20 between September 1995 and April 1996 and then switched to Ultrase MT 18. After four months of therapy with Ultrase® MT 18, the boy began to experience periumbilical cramping. A right hemicolectomy was performed and histopathology revealed the diagnosis of fibrosing colonopathy (Fallick et al, 1997). In March 1997, the child was found by an open bottle of nail polish remover and the mother, believing the child had ingested some of it, administered syrup of ipecac. The patient began to vomit and continued to do so intermittently for 36 hours. He then suffered a cardiac arrest and died. The cause of death was given as mesenteric ischemic small bowel volvulus secondary to postoperative adhesions. The physician believed that there was no causal relationship between the use of a pancreatin and the child's death (PANC002970012).

- A nine-year-old cystic fibrosis female was treated with Zymase® from March 1993 until September 1993 and then switched to Ultrase MT (up to 58,000

lipase units/kg/day) for 16 months until November 1994. Zantac was prescribed in September 1994 presumably for abdominal symptoms and Ultrase® MT was switched to Creon® 20 (27,000 lipase units/kg/day) one month later. Cotazym® was added to her regime in April 1997. Her family relocated in 1997 and a new pediatrician saw her in September 1997, who suspected that her persistent problems with malabsorption, abdominal pain and diarrhea could be due to fibrosing colonopathy. A barium enema in April 1998 showed colonic strictures and a subtotal colectomy was performed. Fibrosing colonopathy was confirmed on histopathology (PANC002980008).

- A five-year-old cystic fibrosis female started treatment with Creon and then switched to Nutrizym® GR in late infancy. At age 2.5 years, she switched to Nutrizym® 22 and remained on high doses of this brand (up to 36 capsules per day) for 2.5 years when she presented with frequent soft stools and fecal soiling. An ultrasound showed free fluid in the peritoneal cavity and increased colonic wall thickness. The barium enema appearances were suggestive of fibrosing colonopathy. Nutrizym® 22 was discontinued and the child was switched back to Creon (O'Keefe, 1996; PANC000980002).

Two cases of DIOS were reported in patients on Creon:

- A CF male has received treatment with Creon since birth at a dose < 1000 units/kg/day. At age 13 years he presented with a 7-year history of abdominal pain. On examination he was found to have a mass in the right iliac fossa. US was suspicious for intussusception and barium enema revealed a colonic stricture. At surgery a stricture of ascending colon was resected. The histology was consistent with DIOS.
- A 17-year-old CF female on Creon 5000 lipase units/kg/day presented with a 5-month history of nausea, abdominal pain bloating and intermittent loose stools. A diagnosis of DIOS was made. Symptoms persist despite adjusting the enzyme dose and changing her diet. Creon was switched to Pancrease (PANC00399002024).

The last case reported as intestinal obstruction was a premature infant born with an intestinal volvulus that was corrected with surgery. At one month, following diagnosis of CF, treatment was commenced with Creon® 12,000 one capsule daily. Six days latter the infant developed narcotizing enterocolitis with multiple perforations on a bowel loop with volvulus. An ileostomy was created at surgery (PANC003990001).

There was one report from literature with colitis. A specific product was not referenced:

- A 6-year-old girl, with insulin-dependent diabetes and hypothyroidism presented with severe diarrhea due to exocrine pancreatic insufficiency. Six months after increasing the dosage of pancreatic enzymes of unknown brand up to 20,000 U lipase/kg/meal rectal bleeding occurred and colonoscopy

showed lesions and infiltration with eosinophile. Upper endoscopy revealed celiac disease. Gluten-free diet did not succeed in symptoms relief but only withdrawal of pancreatic enzymes (LIoyd-Still, 1996; PANC003990084).

Sponsor's Summary and conclusions
The sponsor concluded that there were no cases of histologically confirmed fibrosing colonopathy in which Creon was taken alone were reported. The cases of distal intestinal obstruction syndrome and enterocolitis are not considered to be related to treatment with Creon.

Reviewer's comment: The pathogenesis of fibrosing colonopathy (FC) remains uncertain. In one previous case-control CF study, a significant association between the use of certain types of high-strength (>20,000 units lipase) enzyme preparations and fibrosing colonopathy has been reported[1]. More recently, results of another case-control CF study, conducted by the Cystic Fibrosis Foundation in collaboration with FDA in the US were published[2]. Unlike the previous study, this study found a strong dose-response relation between high daily doses of pancreatic enzymes in any form and the development of FC. Further, the study indicated that there were no significant differences among brands or between high-and low-strength products. Taylor CJ et al[6] reported a colonic stricture suspicious for fibrosing colonopathy in a child receiving standard Creon® at a dose of 13-15000 units of lipase/kg daily for one year. On contrast examination a stricture in ascending colon was found. Histological evaluation from biopsy with colonoscopy indicated mild lamina propria, edema and minimum focal hemorrhage only. However, there was no surgical resection. The patient was managed conservatively.

The understanding of FC is evolving. In previous reports, FC has been reported exclusively in children with CF. More recently, FC has been reported in an adult CF patient and at least in two cases unrelated to cystic fibrosis (Narrative outlined above in the sponsor's report). In fact, FC was reported in the absence of pancreatic enzyme therapy in one of the two non-CF patients. This patient received Mesalazine containing Eudragit for Crohn's disease. The role methacrylic acid copolymer Eudragit in the pathogenesis of FC has been debated. However, further research is needed to definitively delineate the pathogenesis of FC.

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- Smyth RL et al. Fibrosing colonopathy in cystic fibrosis: results of a case-control study, Lancet 1995; 346:1247-1251
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D. Literature Review

Exocrine pancreatic insufficiency (EPI) is a multi-etiologic clinical condition which gives rise to a number of symptoms. A reduction in pancreatic enzyme output to < 10% of normal is usually needed for maldigestion to occur. The major maldigestion/malabsorption problems in patients with EPI arise from incomplete fat digestion, fewer problems arise from protein and carbohydrate malabsorption.

The diagnosis of EPI is established by either direct or indirect tests. Even though the direct test, secretin stimulation, is the gold standard test, its usefulness is limited due to its invasive and labor-intensive nature. Several indirect tests such as analysis of fecal elastase-I (E-I) as well as fecal chemotrypsin (ChT) and 72-hour fecal fat analyses have been developed. While exogenous enzyme substitution interferes with fecal ChT analysis, it dose not interfere with fecal E-I analysis since E-I is specific for human enzyme. The most frequently employed test is the 72-hour fecal fat analysis. Malabsorption is diagnosed when fecal fat excretion exceeds 7% of the dietary fat ingested (15% for infant < 6 months of age).

In children, cystic fibrosis (CF) is the most common cause of EPI, whereas in adult, chronic alcoholic pancreatitis is the most common cause of EPI. CF is the most common genetic disease in Caucasian population. Approximately 5% of Caucasians are carriers of the defective genes, and one in every 2500 to 3000 newborns develops the disease. Incidence in a non-Caucasian is much rare, with estimates around 1 in 20,000 in blacks and 1 in 100,000 in Orientals. It is an autosomal recessive inherited disorder characterized by chronic obstructive pulmonary disease with proximal bronchiectasis often resulting in lung failure and by EPI with maldigestion resulting in severe malnutrition. Obstructive plugging of small pancreatic ducts by viscous secretion begins in utero, leading to the destruction of acinar cells, presumably by the release of lytic enzymes. About half of CF patients have evidence of EPI at the time of birth. Data from the US-CF Registry, including more that 20,000 CF patients showed that 71% were diagnosed with EPI during the first year of life. Prior to the establishment of a network of special CF centers in 1960s, CF was almost universally fatal in early childhood. During the past three decades, improvement in the treatment of

pulmonary infection and malnutrition has extended the median survival of CF victims in the U.S. to about 28 years.

Chronic pancreatitis (CP) affects about 4.7/100,000 of adult population. The majority in the US and Europe are associated with alcohol ingestion. About 15% are idiopathic and other causes are rare. CP is characterized by recurrent or persistent abdominal pain and EPI at a late stage. Morphologically, the pancreas shows an irregular sclerosis with focal, segmental or diffuse destruction of the parenchyma. Abnormalities of the pancreatic duct system as well as intraductal plugs containing protein or calculi are frequent findings.

The cornerstone of therapy for maldigestion due to EPI is replacement of pancreatic enzymes in the gut to allow for efficient digestion and absorption of nutrients. Porcine or bovine enzyme extracts have been used for decades (> 70 years) to provide pancreatic enzymes. Pancreatic enzyme supplements were first marketed in the form of powder, tablets and capsules and were made up from porcine pancreatic extracts containing lipase, amylase and protease. There are a great number of non-enteric and enteric-coated pancreatic enzyme preparations such as capsules and tablets, or in multiunit doses such as pellets, granules and micro tablets. Pancreatic enzyme supplements formulated as microshperes and micro-tablets coated with an acid resistant film to prevent inactivation of enzymes by gastric acid were introduced in the 1970's.

There are a number of enzyme products available commercially, both as prescription or over-the-counter. However, the limitation with enzyme product is that they may vary in terms of potency and pharmaceutical properties. Further, since the enzyme activities vary from product to product the relative potencies across products are not easily comparable which makes it difficult to calculate equivalent doses.

Selection of an enzyme preparation is to be based on the protease concentration within the preparation, the stability of the enzyme in withstanding gastric acidity, and the timely release of the enzyme in the duodenum from the capsules. From all pancreatic enzymes, lipase is destroyed more easily than trypsin. With non-enteric preparation up to 90% of enzyme activity may be lost, and patients may need to take a large quantity of the drug. Concomitant use of proton-pump inhibitors or H2 receptor antagonists has been recommended to suppress gastric acid secretion. Enteric-coated preparations were designed to prevent acid inactivation within the stomach, and the polymer coating of these preparation dissolves at pH >5.

According to some studies encapsulated enteric-coated Microshperes or Minimicrospheres are now considered the enzyme treatment of choice. After release from the gelatin capsules, the enteric-coated pancreatin particles distribute within stomach and mix with the chyme to pass the pylorus together with solid food, particles must be approximately 1.4 mm in diameter. An effective enzyme

preparation must show rapid release of enzymes once a pH of 5.5 has been reached.

There is a considerable individual variation in enzyme production in patients with EPI and consequently, some patients need large amounts of exogenous enzymes and others small amounts of enzymes to have therapeutic benefit. In general practice, the effectiveness of treatment is controlled by clinical symptoms; however, if treatment responses are unsatisfactory, objective assessment of treatment efficacy is needed with quantitative fecal fat excretion test or coefficient of fat absorption (CFA), which assesses the effectiveness of lipase supplementation.

In approaching therapy for EPI, it has been reported that the maximal postprandial delivery of pancreatic lipase in a normal state is approximately 140,000 IU per hour for four hours after a meal, and maldigestion supervenes only when < 5% to 10% of the normal maximal enzyme output is delivered to the duodenum. To meet this requirement, approximately 30,000 units of lipase must be delivered to the duodenum during the prandial and 4-hour postprandial period with each meal for adequate digestion of fat. In non-CF patients, dose is generally initiated with a minimum amount of enzyme (30,000 IU of lipase) with each meal and is subsequently adjusted according to the individual need. Usually, half the standard dose is given with snack. The protein maldigestion appears to be adequately corrected by enzyme replacement therapy, whereas fat maldigestion is hardly ever corrected (normalized) in most patients.

For CF patients, the dosing is administered according to the US Cystic Fibrosis Foundation Consensus Conference recommendations. Enzyme dosing begins with 1000 lipase units/kg per meal for children < age 4 years and 500 lipase units/kg per meal for >4 years. Dose is adjusted as needed within a range of 500 to 2500 lipase units/kg per meal. Doses > 6000 lipase units/kg per meal have been associated with colonic strictures in children < 12 years of age, whether standard-strength enzymes or high-strength pancreatic enzymes were taken.
In general, enzyme preparations are considered to be safe. However, rare but a serious complication such as fibrosing colonopathy has been reported in CF patients, particularly in children receiving a high daily dose (>6000 lipase units/kg per meal) of pancreatic enzyme preparations in any strength or brand.

The pathogenesis of fibrosing colonopathy (FC) remains uncertain. In one previous case-control CF study, a significant association between the use of certain types of high-strength (>20,000 units lipase) enzyme preparations and FC has been reported[13]. More recently, results of another case-control CF study, conducted by the Cystic Fibrosis Foundation in collaboration with FDA in the US were published[14]. Unlike the previous study, this study found a strong dose-response relation between high daily doses of pancreatic enzymes in any form and the development of FC. Further, the study indicated that there were no significant

differences among brands or between high-and low-strength products. Taylor CJ et al[17] reported a colonic stricture suspicious for fibrosing colonopathy in a child receiving standard Creon® at a dose of 13-15000 units of lipase/kg daily for one year. On contrast examination a stricture in ascending colon was found. Histological evaluation from biopsy with colonoscopy indicated mild lamina propria, edema and minimum focal hemorrhage only. However, there was no surgical resection. The patient was managed conservatively.

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V. Clinical Review Methods

A. How the Review was conducted

The reviewer has approached this submission first by focusing upon what the sponsor has requested, and what evidence has been submitted in support of that request. The materials reviewed include all volumes pertinent to clinical trials with emphasis on the protocols and clinical study reports.

This review followed a stepwise fashion directed to determine the factual clinical evidence to support the sponsor's proposed use of Creon® Minimicrshperes® for two indications, i.e. steatorrhea due to PEI associated with CF and CP. The three clinical trials were examined in the following order: First S2233101, followed by S2233102 and then 232.2.01. For each trial, the protocol was examined first, and then the reported data for each trial were assessed for efficacy and safety. The reviewer's final judgment on safety and efficacy for the proposed indication was based on the safety profile of the test drug and whether the stated primary objective endpoint was achieved.

Overall structure for the review includes a tittle page, identifying the sponsor, the drug product, dates of submission and review. The organization of the review and a roadmap to its sections are found in a Table of Content.

B. Overview of Materials Consulted in Review

- Vol. 17, vol. 20 to 35, vol. 57, 58 and 59, amended vol. 1, 2, 3 and 4 were carefully examined. These volumes included information on pivotal study protocols, efficacy results, safety, patient tabulation and CRFs.
- Most of the several amendments submitted by the sponsor from December 2001 to the most current amendment dated August 7, 2003.
- Previously submitted IND 47-546 by this sponsor for the proposed product.
- Previously approved pancreatic enzyme drug product Cotayzm, immediate release, NDA 250-580.

- The US CF Foundation Guidelines for management of exocrine pancreatic insufficiency in patients with cystic fibrosis, and related articles.
- Pre-NDA meeting minutes.
- FDA "Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", US department of HHS, FDA, CDER, CBER, May 1998.
- FDA Draft "Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products-Submitting NDAs", US department of HHS, FDA, CDER, March 2003.
- The most current Physician Desk Reference (PDR)

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Since the trials were conducted in many centers, three centers with relatively larger number of study subjects were chosen for inspection by the Division of Scientific Investigation (DSI). The following report was received on August 26, 2003 from the DSI:

Site # 1. Cleveland, Ohio. Rainbow Babies Children's Hospital (R Stern, M.D.)
Site # 2. Denver, Colorado. The Children's Hospital (Jeff Wagner, MD.)
Site # 3. Iowa City, Iowa. Department of Pediatrics, Univ. of Iowa Hospital and Clinics (Richard Ahrens, M.D.)

A. Protocol S2233101
Site #1:
Few violations were observed 1) Inadequate informed consent forms which failed to describe possible risks from the drug mainly, ileo-cecal strictures, diarrhea, nausea, vomiting, allergic reactions, and hyperuricemia, 2) Two subjects did not continue in the double-blind period with the same dose determined during the open-label period and one subject participated in the double blind period after 19 days from participating in an ibuprofen study.
Site #2:
Three violations: 1) Failure to prepare and maintain accurate case histories which included the dose recorded in the CRF did not always agree with the patient hospitalization charts for 4 subjects, 2) not all medications given in the CFRs were recorded in the chart, 3) Drug disposition records were not accurate for three subjects.
B. Protocol # S2233102
Site # 3:
History of steatorrhea as diagnosed by 72-hrs stool samples was not demonstrated with the exception of 2 subjects.

The overall assessment of findings and general recommendation by DSI stated that the available documentation shows that the violation described do not affect the reliability and validity of the data.

Note: This reviewer noted earlier the incompleteness of the consent forms in most centers with respect to issues related to drug dosing as well as issues on fibrosing colonopathy in CF patients.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Yes, although the following is worth mentioning:

During a careful review of CF protocols, this reviewer identified the sponsor's lack of adopting the guidelines developed by the US CF Foundation Consensus Conference with respect to dosing issues in CF patients (this issue has been addressed by this reviewer in detail elsewhere). Subsequently, the reviewer requested consent forms for review and regrettably only few of the consent forms addressed the maximum allowable dose as well as the risk of fibrosing colonopathy.

E. Evaluation of Financial Disclosure

Solvay Pharmaceuticals submitted NDA 20-725 for Creon® Minimicrospheres® on July 31, 1997. The pivotal studies submitted in support of the NDA were completed prior to the FDA financial disclosure requirements published in Feb 2, 1999. Subsequently, the requirement for financial disclosure was waived for these studies.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusion

In the current NDA 20-725, the sponsor is seeking approval of Creon® Minimicrospheres® for treatment of steatorrhea in patients with EPI. In support of this request, the sponsor evaluated the efficacy of enteric-coated, delayed release, Creon® Minimicrospheres® capsules in two clinical trials for the indication of steatorrhea in adult and pediatric/adolescent CF patients and one clinical trial for the indication of steatorrhea in CP patients, in which the Coefficient of Fat Absorption (CFA) was measured as the primary efficacy variable. The sponsor concluded that the efficacy of the drug product is demonstrated in the three well-controlled clinical trials.

This reviewer's conclusion on efficacy will be addressed under section VI subsection D (efficacy conclusion). Briefly, the efficacy results in three controlled trials achieved the goal stated in the study protocols, i.e. statically significant outcome on the efficacy parameters at a 5% level of significance. In these studies, the proposed drug product achieved a satisfactory response such that the mean CFA increased to 87% from the baseline CFA as low as 50%. However, the efficacy in CF studies has shown to be robust ($p<0.001$) with a considerable degree of reproducibility across both studies. Whereas, in CP study, even though the proposed drug has achieved a statistically significant efficacy outcome, the primary efficacy result has not shown to be robust ($p=0.019$) for a single and small study to claim efficacy. Nonetheless, it is reasonable to

consider the CF efficacy results to support the efficacy in CP study given the close relation of the condition being treated, i.e. steatorrhea due to EPI in both populations.

B. General Approach to Review of the Efficacy of the Drug

The reviewer approached this submission first by what the sponsor has requested, and what evidence has been submitted in support of that request. The review of efficacy was on the data submitted in the aforementioned three pivotal trials for two indications, i.e. cystic fibrosis and chronic pancreatitis. Each of the submitted trials was examined in detail, starting with the protocol, amendments, data gathering methods (CFR), the primary outcome measure of efficacy chosen, statistical methods planed for analysis of data, the characteristic of patients chosen for study, rationale for dose selection. Following careful examination of the protocol, the results were examined in equally great detail. The reviewer's comment and conclusion were incorporated as deemed appropriate. The three pivotal trials were reviewed in the following order: First S2233101, followed by S2233102 and finally 223.2.01. Each trial starts with a summary of protocol followed by efficacy analysis results. The reviewer's comment on efficacy results for all trials combined is addressed under section VI., subsection D.

C. Detailed Review of Trials by Indication

As summarized in Table 3, the sponsor submitted three clinical trails for two indications, i.e. for steatorrhea due to EPI in pediatric/adolescent (S2233101) and adult (S2233102) CF patients and in CP patients (223.2.01).

Table 3. Summary of three pivotal trials in U.S. (Reviewer's Table)

Protocol #	Study site #	Population	Drug product	Design	Total Patient enrolled	Total Patient randomized	Total Patient Completed
S2233101	6	CF (pediatric /adolescent)	Creon®20	Parallel, Double-blind, Placebo controlled	47	38	37
S2233102	6	CF (adult)	Creon®20	Parallel Double-blind, Placebo-controlled	50	36	34
223.2.01	16	Chronic Pancreatitis	Creon®10	Parallel Double-blind, Placebo controlled	64	27	27

1. <u>Protocol S2233101 (pediatric and adolescence cystic fibrosis)</u>

(a) The following is a summary of the protocol (vol. 1.20, page 1129):

Title: A comparison of the efficacy and safety of Creon® 20 and placebo in the treatment of steatorrhea in pediatric and adolescent CF patients with EPI.

Six study sites:

- Rainbow Babies and Children Hospital, Cleveland, OH (Dr Robert Stern);
- Oregon Health Sciences University, Portland, OR (Dr Jay Eisenberg);
- The Children's Hospital, Denver, CO (Dr Jeff Wagener);

- University of Iowa Hospital and Clinics, Iowa City, IO (Dr Richard Ahrens);
- University of Wisconsin, Madison, WC (Dr Michael Rock);
- Children's Hospital, Pittsburgh, PN (Dr Davis Orenstein). The sponsor stated that these centers were selected from U.S. Care Centers listed in the CF Foundation Directory.

Objectives

Primary objective: To compare the effectiveness of Creon® 20 (20,000 lipase units, USP) Minimicrospheres® capsules to placebo in the treatment of steatorrhea in CF patients with EPI who were maintained on a high fat diet.

Secondary objective: To compare the effects of treatment on frequency of bowel movement, stool consistency, clinical global improvement (CGI) and safety following administration of Creon® 20 capsules

Efficacy parameters

The primary efficacy parameter was the Coefficient of Fat Absorption (CFA) which was calculated from 72-hour stool values and fat intake data from nutritional diaries according to the following formula: $CFA\% = \frac{\text{Fat intake (g/day)} - \text{Fat excretion (g/day)}}{\text{Fat intake (g/day)}} \times 100$

The primary efficacy measure was change from baseline (open-label) to final (double-blind) assessment in the CFA. A total of two 72-hour stool collections were scheduled.

The secondary efficacy parameters measured the change from open-label Creon® 20 treatment to double-blind treatment for number of bowel movements as well as most frequent reported stool consistency per stool collection period, and clinical global improvement (CGI).

Patients were instructed to record stool consistency and number of bowel movements on a daily stool diary during both stool collection periods. Stool consistency was rated by the patient as follows: 1 = hard; 2 = formed/normal; 3 = soft; 4 = watery.
CGI was assessed by a physician at the end of the double-blind treatment phase using a 7-point physician rated scale as follow: 0 = not assessed; 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse.

Safety parameters were to be summarized by treatment group and included physical exam and vital signs, routine clinical laboratory examination including urine and serum uric acid monitoring and adverse events.

Study design

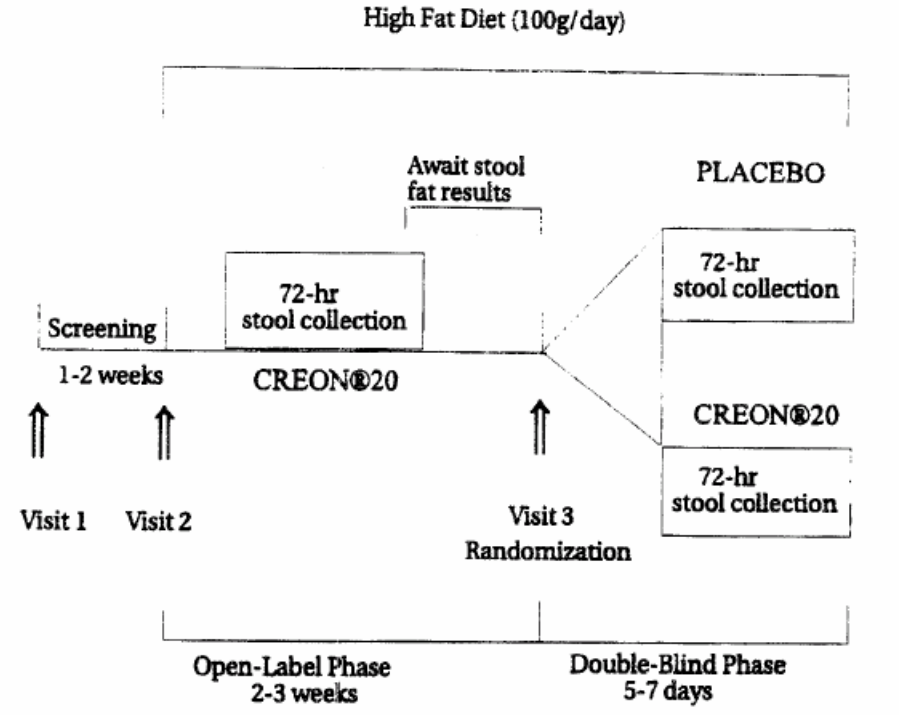
The study design was randomized, double-blind placebo-controlled, parallel group, and multicenter study with an open-label run-in phase. A minimum of 40 evaluable patients was

expected to complete the double-blind treatment phase. (Scanned Figure 1, Vol. 20, page 1049)

Following a one- to two-week screening period, qualified patients entered the open-label phase of the study where they began a controlled high-fat diet (at least 100 g /day) while individually adjusting the number of Creon® 20 capsules per meal (snack) to maximize clinical effect as guided by clinical symptoms. When an optimal dose was reached and maintained for at least two days, and after at least three days on the high-fat diet, patients entered the clinic to begin a 72-hour stool collection, during which time the high fat diet was strictly controlled. During stool collection, a stool marker (food dye) was used to determine gastrointestinal transit time.

Based on the value of CFA obtained at the end of open-label phase, patients were either excluded from further participation in the study (CFA ≤ 80%), or entered in the double-bind phase (CFA was >80%). Qualified patients were randomized to either Creon® 20 or placebo treatment. The double-blind dose was the same as that established during open-label treatment. After a minimum of two days of double-blind treatment while on a high-fat diet, patients were admitted to the clinic for the second 72-hour stool collection as shown in Figure 1.

FIGURE 1.
Study Design



Randomized patients were assigned the lowest available double-blind patient number, in sequential order, from the randomization schedule provided by the sponsor. Randomization scheme and codes are presented in sponsor's Appendix 1.5 (volt 20, page 1326).

- **Inclusion criteria:**
  - Males and females 7 to 18 years old.
  - Females of childbearing age were required to have a negative serum pregnancy test.
  - Have a diagnosis of CF documented by sweat chloride results > 70 mm/l and clinical symptoms of exocrine pancreatic insufficiency with a history of steatorrhea.
  - Stabilized on diet and dose of pancreatic enzyme supplementation which provides satisfactory symptom control for one month or more as documented by medical history and information collected from the patient during the screening period.

- **Exclusion criteria** (pertinent):
  - Acute gastrointestinal illness, uncontrolled steatorrhea.
  - History of intestinal resection or history of recurrent distal intestinal obstruction syndrome

- Extreme Cachexia (percent of ideal weight <60% of predicted).
- Acutely exacerbated pulmonary disease or severe respiratory impairment (FEV_1<25%)
- Ingestion of medium chain triglycerides as nutritional supplement.
- Abnormal serum uric acid values at screening.
- Concurrent use of non-study pancreatic enzyme supplement, antacid, acid suppressant, prokinetic drugs, or antibiotics that has caused diarrhea in the past.

Reviewer's comment: As judged by the inclusion/exclusion criteria, the study population was adequate for the proposed CF study.

Concomitant therapy

Drugs known to affect blood urinary uric acid concentrations were prohibited during the study (e.g. aspirin, diflusinal, allopurinol, probenicid, thiazide, diuretics, phenylbutazone, sulfinpyrazone)

Study medication and dose selection

Each Creon® 20 capsule contains, 20,000 USP units lipase, 66,400 USP units Amylase and 75,000 USP units protease.

The open-label Creon® 20 dose was individualized for each patient while on a high-fat diet using clinical symptoms as a guide. Patients were instructed to adjust the number of capsules taken per meal/snack. The double-blind dose was to be the same as that established during open-label treatment. Patients were instructed to return all unused medication and packaging materials to the clinic staff in a timely manner. A strict accounting of study medication dispensed to, and received from was recorded on the CRF.

Statistical methods

Patient samples

- Intent-to-treat (ITT) population was defined as all patients who were randomized into the double-blind phase of the study and took at least one dose of study medication. ITT patients were to be used for efficacy analysis.
- Total patient population was defined as all patients enrolled into open-label phase of the study that took at least one dose of open-label study drug. Total patient population was to be used for safety analysis.
- Evaluable population was defined as patients who had both baseline and final CFA.

The primary efficacy parameter, change from open-label to double-blind CFA, was analyzed by fixed-effects analysis of variance (ANOVA) on treatment, center and treatment-by-center interaction to test the null hypothesis that mean change from baseline CFA in the Creon® 20 group is equal to that of the placebo group. If appropriate, analysis of covariance using appropriate covariates was to be performed. Treatment comparisons were considered statistically significant if $p \leq 5\%$ using two-sided tests.

With 40 evaluable patients (20 per treatments), 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 and placebo.

For secondary efficacy parameters, change in stool frequency (between open-label to double blind) was analyzed using ANOVA. Change in the most frequently reported stool consistency and CGI were analyzed with Cochran-Haenszel row mean scores test, controlling for center.

Analysis of safety parameters were conducted in all patients enrolled into the open-label phase of the study who took at least one dose of open-label study drug were included in the safety analyses.

Reviewer's comment: Overall, the protocol appeared to be well designed. It should be noted that in CF protocols, the sponsor did not adapt the guidelines developed by the U.S. Cystic Fibrosis Foundation Consensus Conference in 1995. For CF patients pancreatic enzymes dosing are determined by individual body weight and age within the recommended dose range of 500 to 2500 lipase units/kg/meal. Enzyme supplements > 6000 lipase U/kg/meal have been associated with fibrosing colonopathy in pediatric cystic fibrosis patients. In this protocol the upper limit of lipase units per day was not specified. Patients were instructed to adjust the dose on their own without any further instruction on the maximum allowable dose.

The applicant did not provide a satisfactory response to the request made on July 18, 2003 by this reviewer in this regard. The applicant's response in its words "The 1995 guidance was not taken into account for study drug dosing individualization. The study was already running at the time the guidance was published. Solvay did not amend the protocol to specify the upper limit of lipase units per day. This was left to the investigator's clinical judgment" (Amendment dated August 7, 2003, 1 of 1, page 4). It must be assumed that the sponsor as well as the investigators who are expertise in the field are familiar with the consensus conference recommendation that took place in March 1995, four months before the pediatric CF study was initiated in July 1995.

(b) Results (vol. 20, page 1080)

Disposition of patients

The study was initiated in July 13, 1995, and ended in March 22, 1996

- A total of 47 patients enrolled at six centers into open-label phase.
- A total of 11 patients discontinued prematurely from the study (Appendix 2.2 vol. 20, page 1344).
- Nine patients discontinued from the open label phase; 7 of who did not qualify for randomization into double-blind phase (CFA <80%), and the remaining 2 withdrew consent.
- 38 patients randomized to double blind phase (20 placebo and 18 Creon 20), but two discontinued prematurely. Patient # 60207 withdrew from the study due to stomach discomfort and patient # 60196 withdrew consent. Both patients were randomized to placebo treatment arm.
- 37 patients were included in the final analysis and 36 patients completed the study as summarized in Table 3 of this review.

Two Appendices, 2.1 and 2.2 listing all patient disposition by site and treatment center, including patient identifier, reason for discontinuation and duration of treatment at discontinuation are presented in vol. 21, page 1344).

Protocol deviation

Sixteen patients were found to have protocol deviation, 7 placebo and 9 Creon patients. Nearly half of these patients had minor deviations that may have not influenced the sponsor's efficacy analysis. Eight patients had some irregularities in 72-hour stool collections (4 patients in each arm). A description of each protocol deviation is summarized by treatment arm for the ITT study population in sponsor's Table 3, vol. 20, page 1081.

Reviewer's comment: As per the reviewer's request, the statistician, Dr Chen, performed additional efficacy analysis, by excluding 8 patients with protocol deviation due to irregularities with stool collections. However, the result still holds statically significant difference between the treatment groups ($p < 0.001$). The reader may refer to reviewer's comment under subsection efficacy results in this study for more information.

- **Demographics**

Thirty-eight patients, 18 males and 20 females between 7 and 17 years of age made up the ITT patient sample. Enrolled patients ranged in weight from 20 kg to 59 kg and in height from 112 cm to 170 cm. The majority of patients (95%) were Caucasian. There was no significant difference between the treatment groups for age, gender, race, height or weight. The mean age in placebo group was 12.8 years with 55% male, 45% female and 100% Caucasian. The mean age for Creon® 20 group was 12 years with 39% male, 61% female and 89% Caucasian (one patient was Negroid and mixed race). Table 4 summarizes the demographic characteristics of ITT patients

Table 4. Demographic data of ITT patients (Reviewer's Table)

Patient characteristics	Double-blind treatment			p-value*
	Placebo (n = 20)	Creon ®20 (n =18)	Total (n = 38)	
Gender				
Male	11 (55%)	7 (39%)	18 (47%)	0.181
Female	9 (45%)	11 (61%)	20 (52%)	
Race				
Caucasian	20 (100%)	16 (89%)	36 (95%)	0.323
Negroid	-	1 (6%)	1 (2%)	
other	-	1 (6%)	1 (2%)	
Age (yrs)				
Mean ± SEM	12.8 ± 0.6	12.1± 0.7	12.5 ± 0.5	0.98
[range]	[8.2- 17.9]	[7-17.5]	[7-17.9]	
Height (cm)				
Mean ± SEM	147.8 ± 3.0	145.6 ± 4.0	146.8 ±2.4	
[range]	[118.1-168.7]	[112.8-169.8]	[112.8-169.8]	
Weight (kg)				
Mean ± SEM	39.2 ± 2.4	36.8 ± 2.4	38.0 ±1.7	0.537
[range]	[22.4- 59.0]	[20.8-59.0]	[20.8-59]	

* p-value is based on Cochran-Mantel-Haenszel, controlling for center.

Reviewer's comment: Caucasian predominance in this study is representative for the disease. The incidence of CF in Caucasian population is estimated as one in every 3000 live birth. Incidence in non-Caucasian is much rear, with estimates around 1 in 20,000 in blacks and 1 in 100,000 in Orientals (Corey, M. et al. J.Clin Epidemiology, 1988). The age of the study population may not be representative of CF patients in general. The majority of CF patients are affected by this condition at much younger ages including newborns and toddlers.

Medical history

The clinical report included two appendices, 2.3 and 2.3.1, (vol. 21 page 1349), listing detailed medical history, patient identifier, center, randomized /non-randomized patients. History of steatorrhea and lung disease consistent with cystic fibrosis was present in all patients enrolled. Other commonly reported conditions were nasal polyps, and otitis media.
The ITT patient sample appeared to be representative of the general pediatric and adolescent population diagnosed with cystic fibrosis with no apparent differences between the two treatment groups.

Drug Dosage and Duration of Exposure

Note: Dose was individualized for each patient while on a high-fat diet using clinical symptoms as a guide. For each study phase drug dosage was calculated for each patient as the mean number of capsules taken per day multiplied by the lipase content per capsules (20,000 units) divided by the body weight (kg) at the screening visit.

During open-label treatment and double-blind treatment phases, the daily mean lipase units/kg was comparable between treatment groups. During open-label phase, the mean Creon® 20 dose was 7340 lipase units/kg/day (1364 to 15497) for placebo group and 7440 lipase units/kg/day for Creon® 20 group (1280 to 14983). During double-blind treatment phase, the mean Creon® 20 dose was 7855 lipase units/kg/day (1081 to 15782) for patients receiving Creon® 20 and placebo patients received capsules equivalent to the actual mean lipase dose (7560).

The mean duration of exposure to the test drug was comparable between the two treatment groups during each treatment phase. During open-label phase, the mean duration of exposure to Creon® 20 was 18 days for both treatment groups. The mean duration of exposure to placebo or Creon® 20 was similar (7 days) during double-blind treatment phase.

Reviewer's comment: Even though in this study the doses received happened to fall within the recommended dose range, i.e. from 500 to 2500 lipase U/kg/meal, the upper limit was not specified in the protocol. Notable in this study is the wide variation of the doses used, i.e. from as low as 1081 lipase units/kg/day to as high as 15782 lipase units/kg/day. This is consistent with the wide individual variation in enzyme production in patients with EPI.

A summary of mean dosage and duration of exposure is shown in Table 5 (Sponsor's Table 9 and 10, vol. 20, page 1091-1092). Appendices 2.9 and 2.10 (vol. 21, page 1470) present duration of exposure and drug dose for total patient sample.

Table 5. Drug dosage and duration of exposure in ITT patient (Reviewer's Table)

	Open-label Treatment*		Double-blind Treatment	
	Placebo (n=20)	Creon®20 (n=18)	Placebo (n=20)	Creon®20 (n=18)
Dosage (lipase units/kg/day)				
Mean	7339.98	7440.45	7650.68	7855.66
Standard Error	854.36	881.45	878.15	1032.80
Minimum	1364.30	1280.00	881.15	1081.77
Maximum	15497.45	14983.97	15561.22	15782.93
Duration of exposure (days)				
Mean	18.05	18.17	7	6.94
Standard Error	1.24	1.99	0.30	0.13
Median	15.5	15	7	7
Minimum	13	9	3	6
Maximum	31	46	10	8

* All patients received Creon® 20 during open-label treatment, sample is broken down by double-blind treatment assignment for comparison

Results of Efficacy Analysis

The primary efficacy parameter was the change in CFA from open-label to double-blind treatment. There were 38 ITT patients one patient #60207 was excluded from analysis due to missed stool data. Therefore, 37 patients completed the study (19 placebo and 18 Creon20).

The efficacy results from this study demonstrate statistically significant treatment differences between Creon®20 and placebo for the primary efficacy parameter (change from baseline CFA), and all secondary efficacy parameters (stool frequency, stool consistency, and CGI).

The difference between the two treatment groups in the change in mean CFA (primary endpoint) from open-label to double-blind treatment was highly significant ($p<0.001$). The mean CFAs of the placebo and Creon® 20 treatment groups were comparable after open-label Creon® 20 treatment (86% and 87%, respectively). After double-blind treatment, the mean CFA for the placebo group decreased by 34 percentage points to 52%; in contrast, the mean CFA for the Creon® 20 group decreased by only 3 percentage points to 84% ($p<0.001$).

Reviewer's comment: Due to the reviewer's concern with the protocol deviation with respect to irregularities in stool collections identified in 8 patients, additional analysis was performed by Dr. Chen, Statistician reviewer, by excluding these patients from data set. The result remained significant such that the change in mean CFA from open-label Creon® 20 phase to double-blind was –36 for patients randomized to placebo treatment versus –2 for patients randomized to Creon® 20 ($p<0.0001$).

CFA data were summarized by treatment phase and by double-blind treatment assignment. [Table 6 (Sponsor's Table 12, vol. 20, page 1096)].

Table 6. Coefficient of Fat Absorption (CFA) in ITT patients (Reviewer's Table)

	CFA (%)		p-value#
	Placebo (n=19)	Creon®20 (n=18)	
Open-label (OL) treatment*			
Mean ± SEM	86.64 ± 1.02	87.36 ± 1.14	
[Range]	[82.21 – 99.05]	[80.40 – 94.89]	
Double-blind (DB) treatment			
Mean ± SEM	52.15 ± 5.61	84.11 ± 2.22	
[Range]	[17.5 – 99.05]	[57.14 – 98.27]	
Change from OL to DB treatment			
Mean ± SEM	-34.49 ± 5.14	-3.25 ± 1.82	<0.001
[Range]	[-70.17 - 6.20]	[-29.57 - 4.31]	

* All patients received Creon20 capsules during open label treatment, however, sample is broken down by double-blind treatment assignment for comparison. # p-value is based on ANOVA.

As summarized in Table 7, the sponsor analyzed results of fat intake and fecal fat excretion, the two parameters on which the CFA value was based. There was no significant difference in fat intake between treatments in both phases (p=0.49). There was no apparent difference in fecal fat excretion between the placebo and Creon® 20 groups during open-label treatment with Creon® 20 (16 .8 and 16.6 g/day, respectively). In contrast, there was significantly greater (p=0.001) increase in mean fecal fat excretion in the placebo group (62 g/day) after double-blind placebo treatment compared with the Creon® 20 group (16.8 g/day) after the open-label Creon® 20 treatment.

Table 7. Fat intake and fat excretion in ITT patients (Reviewer's table)

	Fat gram/day		p-value#
	Placebo (n=19)	Creon®20 (n=18)	
Daily fat intake			
Open-label (OL) treatment*			
Mean ± SEM	139.13 ± 12.76	128.26 ± 8.00	
[Range]	[86.80 - 314.30]	[88 – 188]	
Double-blind (DB) treatment			
Mean ± SEM	131.41 ± 9.91	130.16 ± 9.81	
[Range]	[79.40 - 224.30]	[83.20 - 223.10]	
Change from OL to DB treatment			
Mean ± SEM	-7.73 ± 8.59	1.91 ± 4.98	0.494
[Range]	[-148.60 – 36.10]	[-38.20 - 64.90]	
Daily fecal fat excretion			
Open-label Treatment*			
Mean ± SEM	16.83 ± 1.55	16.66 ± 1.97	
[Range]	[1.70 – 33.00]	[5.20 – 31]	
Double-blind treatment			
Mean ± SEM	62.19 ± 9.53	20.74 ± 2.98	
Range	[1.00 – 150.00]	[1.70 – 45.00]	
Change from OL to DB treatment			
Mean ± SEM	45.37 ± 8.41	4.08 ± 1.89	0.001
[Range]	[-12.30 – 117.00]	[-6.00 – 27.00]	

* All patients received Creon20 capsules during open label treatment, however, sample is broken down by double-blind treatment assignment for comparison. # p-value is based on ANOVA with factors for center, treatment, and their interaction

Secondary efficacy parameters:

Stool frequency and consistency were collected on stool diaries during the inpatient portion of each treatment phase. Data listings and summaries for stool frequency and consistency are provided in Appendices 2.14 and 2.15, vol. 24. Clinical Global Improvement (CGI) data listing and summary are provided in appendix 2.16, vol. 24.

Table 8 summarizes results of stool frequency and consistency in ITT patients.
The change in the mean stool frequency from open-label to double-blind treatment decreased (-1.2) for patients randomized to Creon® 20 treatment and increased (4.3) for patients randomized to placebo. The difference between the mean change in the two treatment groups was statistical significant (p=0.002).

The most frequently reported stool consistency during open-label phase was "formed" (83% - 89%). Similar percentage of patients (88%) reported "formed" stools following treatment with Creon® 20 during double-blind phase; in contrast, the majority of placebo treated patients (89%) reported "soft" stools and only 5% reported "formed" stools during double-blind phase. The change in consistency from open-label Creon® 20 treatment to double-blind treatment was significantly different between treatments (p=0.001).

Table 8. Stool frequency and consistency in ITT patients (Reviewer's Table)

	Placebo (n=19)	Creon®20 (n=18)	p-value
Stool frequency*			
Open-label stool collection period*			
Mean ± SEM	8.1 ± 0.82	9.22 0.92	
[Range]	[3-17]	[4-17]	
Double blind stool collection period			
Mean ± SEM	12.42 ± 1.32	8.06 ± 0.61	
[Range]	[2-25]	[4-14]	
Change from open label to double-blind			
Mean ± SEM	4.3 ± 1.0	-1.17 ± 0.73	0.002#
[Range]	[-5 – 11]	[-6 – 4]	
Stool consistency			
Open-label stool collection period			
Hard	1 (5%)	1(5%)	
Formed	13 (89%)	15 (83%)	
Soft watery	5 (26%)	2(11%)	
Double blind stool collection period			
Hard	1 (5%)	2 (11%)	
Formed	1 (5%)	16 (88%)	0.001@
Soft	17 (89%)	0	

* All patients received Creon® 20 during open label treatment; however, sample is broken down by double blind treatment assignment for comparison

 # p-value is based on ANOVA with factors for center, treatment and their interaction

@ p-value is based on Cochran-Mantel-Haenszel row mean scores test

For CGI, a 7-point scale was used by the physician to rate each patient's total clinical improvement at the end of the double-blind treatment phase relative to their condition at

baseline. At the end of double-blind treatment 89% of patients in Creon® 20 group rated as either improved or remained unchanged, as opposed to 32% of patients in placebo group ($p<0.001$) (Table 17, vol. 20 page, 1104).

II. Protocol S2233102 (Adult cystic fibrosis)

(a) The protocol for this study is identical to the previous CF study (S2233101) except that the patients in this study were adult patients (≥ 18 years). Further, the study was conducted at the same centers by the same investigators.

Note: Since the design of this study is identical to the previous CF study, comments made in that study by the reviewer may not be repeated.

(b) Results (vol. 24, page 2968)

Patient disposition

The study was initiated in June, 29, 1995 and completed in July 5, 1996
Of fifty patients entered into open-label phase at six centers, 36 were qualified (CFA >80%) for randomization in the double-blind phase (18 placebo and 18 Creon®20). Of the fourteen patients who were not randomized, twelve patients were not qualified (CFA <80%) for randomization and two had adverse event (pulmonary exacerbation in one and constipation/bloating in the other patient).
A summary of patient disposition is shown in Table 9.

Table 9. Summary of patient disposition (Reviewer's Table)

Center Number	Total patient entered open-label phase (n=50)				Total
	Randomized to double- blind phase (n=36)		Not randomized to double-blind phase (n=14)		
	Placebo	Creon®20	CFA <80%	Adverse event	
01	3	2	4	1	10
02	4	4	1	-	9
03	2	2	1	-	5
04	6	6	3	1	16
05	0	1	2	-	3
06	3	3	1	-	7
Total	18	18	12	2	50

- **Demographics of ITT patients**

  Thirty-six patients, 22 males and 14 females between 18 and 53 years of age made up the ITT patient sample. Enrolled patients ranged in weight from 32 kg to 68 kg and in height from 144 cm to 180 cm. All study patients were Caucasians. There was no major difference between treatment groups with respect to, age, gender, height or weight. The mean age of placebo group was 24 years with 67% male and 33% female, the mean height and weight

was 165 cm and 54 kg, respectively. For Creon® 20 group, the mean age was 23 years with 56% male and 44% female, the mean height and weight was 168 cm and 54 kg, respectively. Table 10 summarizes the demographic characteristics for the 36 ITT patients.

Table 10. Demographic data of ITT patients (Reviewer's Table)

Patient Characteristics	Double-blind treatment		Total	p-value[#]
	Placebo (n = 18)	Creon ®20 (n =18)	(n=36)	
Gender				
Male	12 (67%)	10 (56%)	22 (61%)	0.58
Female	6 (33%)	8 (44%)	14 (38.9%)	
Race				
Caucasian	18 (100%)	18 (100%)	36 (100%)	
Age (yrs)				
Mean ± SEM	24.4 ± 2.1	23.3 ± 1.2	23.8 ± 1.2	0.616
[range]	[18.2- 53.5]	[18.5-35.8]	[18-53.5]	
Height (cm)				
Mean ± SEM	165.2 ± 2.2	168 ± 2.1	166.6 ± 1.5	0.181
[range]	[150-180]	[144.8-179.4]	[144.8-180.0]	
Weight (kg)				
Mean ± SEM	54± 2.4	54 ± 1.8	54.1 ± 1.5	0.881
[range]	[32-68]	[43-66]	[32.7-68.0]	

* p-value is based on Cochran-Mantel-Haenszel, controlling for center.

Dosage and duration of exposure

Drug dosage was calculated for each patient as the mean number of capsules taken per day multiplied by the lipase content per capsule (20,000 units) divided by the weight (kg) at the screening visit.

As shown in Table 11, the sponsor reported that the mean dose of study medications were comparable across treatment groups in both open-label and double-blind treatment phases.

During open-label run-in-phase, the mean Creon® 20 dose was 4782 lipase units/kg /day (979-10096) for placebo patients and 4907 lipase units/kg/day (1317 to 12270) for Creon® 20 patients. During-double-blind treatment phase, the mean Creon® 20 dose was 4537 lipase units/kg (1113-10542) for patients receiving Creon® 20, whereas placebo patients received the capsules equivalent to the actual mean lipase units (5107 units/kg/day).

The duration of exposure to Creon® 20 ranged from 10 days to 36 days with a mean of 18 days for patients in open-label treatment. During double-blind treatment, the mean exposure to Creon® 20 was 7 days and to placebo was 6.7 days with a range of 5 days to 8 days.

Table 11. Drug dosage and duration of exposure in ITT patient (Reviewer's Table)

	Open-label Treatment*		Double-blind Treatment	
	Placebo (n=18)	Creon®20 (n=18)	Placebo (n=18)	Creon®20 (n=18)
Dosage (lipase units/kg/day)				
Mean	4782.6	4907.2	5107	4537.8
Standard Error	622.8	765.5	749.9	624.2
Minimum	979.8	1317	1007.8	1113
Maximum	10096.2	12270.1	12454.2	10542.3
Duration of exposure (days)				
Mean	17.3	18.9	6.7	7.1
Standard Error	1.7	1.6	0.2	0.2
Median	14	15	7	7
Minimum	10	13	5	6
Maximum	36	34	8	8

* All patients received Creon® 20 during open label treatment; however, sample is broken down by double blind treatment assignment for comparison.

Results of Efficacy Analysis

The primary efficacy parameter was the change in mean CFA from open-label to double-blind treatment. A total of 36 qualified patients were randomized (18 placebo and 18 Creon® 20) in a double-blind phase and were included in the analysis.

The efficacy results from this study demonstrate statistically significant treatment differences between Creon®20 and placebo for the primary efficacy parameter (change from baseline CFA), and all secondary efficacy parameters (stool frequency, stool consistency, and CGI).

A summary of mean CFA values for both treatment groups is depicted in Table 12.
The results in this study were similar to that of the previous CF study in that the change in mean CFA from open-label to double-blind treatment was highly significant ($p<0.001$). The mean CFAs for the placebo and Creon® 20 treatments were comparable during open-label Creon® 20 treatment (88% and 89%, respectively). After double-blind-treatment, the mean CFA for placebo group decreased by 37 percentage points to 51%; in contrast, the mean CFA for the Creon® 20 group decreased by only 2 percentage points to 87% ($p<0.001$).

Table 12. Coefficient of Fat Absorption (CFA) in ITT patients (Reviewer's table)

	CFA (%)		**p-value[#]**
	Placebo (n=18)	**Creon®20 (n=18)**	
Open-label (OL) treatment*			
Mean ± SEM	87.8 ± 1. 2	89.2 ± 1.1	
[Range]	[80 – 96.8]	[80.9 – 97.9]	
Double-blind (DB) treatment			
Mean ± SEM	50.9 ± 7.3	87.2 ± 1.7	
Range	[-25.1 – 95.7]	[69.2 – 98.4]	
Change from OL to DB treatment			
Mean ± SEM	-36.9 ± 6.7	-2 ± 0.9	<0.001
Range	[-106.17 – 4]	[-11.7 - 4.5]	

*All patients received Creon20 capsules during open label treatment, however, sample is broken down by double-blind treatment assignment for comparison

 # p-value is based on ANOVA with factors for center, treatment and their interaction

As summarized in Table 13, the sponsor analyzed results of fat intake and fecal fat excretion, the two parameters on which the CFA value was based.

Table 13. Fat intake and fat excretion in ITT patients (Reviewer's table)

	Fat gram/day		p-value#
	Placebo (n=18)	Creon®20 (n=18)	
Daily fat intake			
Open-label (OL) treatment*			
Mean ± SEM	151.4 ± 8.2	151.2 ± 8.5	
[Range]	[89.9 - 217.30]	[103.6 – 244.4]	
Double-blind (DB) treatment			
Mean ± SEM	155.6 ± 8.7	145.7 ± 5.9	
[Range]	[78.7- 215.2]	[103.4 - 201.1]	
Change from OL to DB treatment			
Mean ± SEM	4.2 ± 6.9	-5.5 ± 5.1	0.294
[Range]	[-45.8 – 65.1]	[-72.8- 23.2]	
Daily fecal fat excretion			
Open-label (OL) Treatment*			
Mean ± SEM	18.9 ± 2.3	16.8 ± 2.3	
[Range]	[5 – 39]	[3.5 – 41]	
Double-blind (DB) treatment			
Mean ± SEM	80.8 ± 13.6	19.1 ± 3.2	
[Range]	[4.8 – 220]	[2.3 – 62]	
Change from OL to DB treatment			
Mean ± SEM	61.9 ±11.8	2.3 ± 1.4	<0.001
[Range]	[-5.6- 181]	[-7 – 21]	

* All patients received Creon® 20 capsules during open label treatment, however, sample is broken down by double-blind treatment assignment for comparison

 # p-value is based on ANOVA with factors for center, treatment and their interaction

Similar to the previous CF study, the amount of fat ingested was comparable between treatments (p=0.294); in contrast, fecal fat excretion was significantly different between the treatments (p<0.001). There was no apparent difference in fecal fat excretion between the placebo and Creon® 20 treatment during open-label treatment with Creon® 20 (18.9 and 16.8 g/day, respectively). In contrast, there was significantly greater (p<0.001) increase in mean fecal fat excretion in placebo treatment compared with the Creon® 20 treatment (80 g/day vs 18 g/day, respectively).

Secondary efficacy parameters:

Stool frequency and consistency were collected on stool diaries during the inpatient portion of each treatment phase. Data listings and summaries are provided in Appendix 2.14 and 2.15, vol. 24. Clinical Global Improvement (CGI) data listing and summary are provided in appendix 2.16, vol. 24.

Table 14 summarizes results of stool frequency and consistency in ITT patients.
The change in the mean stool frequency from open-label to double-blind treatment decreased (-0.6) for patients randomized to Creon® 20 treatment and increased (6.6) for patients randomized to placebo, this difference was statistically significant (p= <0.001).

The most frequently reported (67% - 89%) stool consistency during open-label Creon® 20 treatment was "formed". Similar percentage of patients reported (67%) "formed" stools following treatment with Creon® 20 during double-blind phase. In contrast, 78% reported "soft" stools and only 22% reported "formed" stools with placebo treatment during double-blind phase. The change in consistency from open-label Creon® 20 treatment to double-blind placebo treatment was significantly different between treatments (p=0.001).

Similarly, the sponsor's data for clinical global improvement (CGI) showed that patients in Creon® 20 group felt significantly better than placebo group (p <0.001) (Table 17, vol. 24, page 2995)

Table 14. Stool frequency and consistency in ITT patients (Reviewer's Table)

	Placebo (n=18)	Creon®20 (n=18)	p-value
Stool frequency			
Open-label stool collection period*			
Mean ± SEM	7.6 ± 0.7	7.2 ± 0.6	
[Range]	[2-15]	[4-14]	
Double blind stool collection period			
Mean ± SEM	14.1 ± 1.7	6.6 ± 0.7	
[Range]	[4-30]	[3-14]	
Change from open label to double-blind			
Mean ± SEM	6.6 ± 1.4	-0.6 ± 0.6	<0.001#
[Range]	[-1 – 22]	[-5 – 5]	
Stool consistency			
Open-label stool collection period*			
Hard	1 (6%)	2 (11%)	
Formed	16 (89%)	12 (67%)	
Soft watery	1 (6%)	4(22%)	
Double blind stool collection period			
Hard	0	2 (11%)	
Formed	4 (22%)	12 (67%)	0.001@
Soft watery	14 (79%)	4 (22%)	

* All patients received Creon20 during open label treatment; however, sample is broken down by double blind treatment assignment for comparison

 # p-value is based on ANOVA with factors for center, treatment and their interaction

@ p-value is based on Cochran-Mantel-Haenszel row mean scores test

III. Protocol 223.2.01 (chronic pancreatitis)

(a) Summary of the protocol

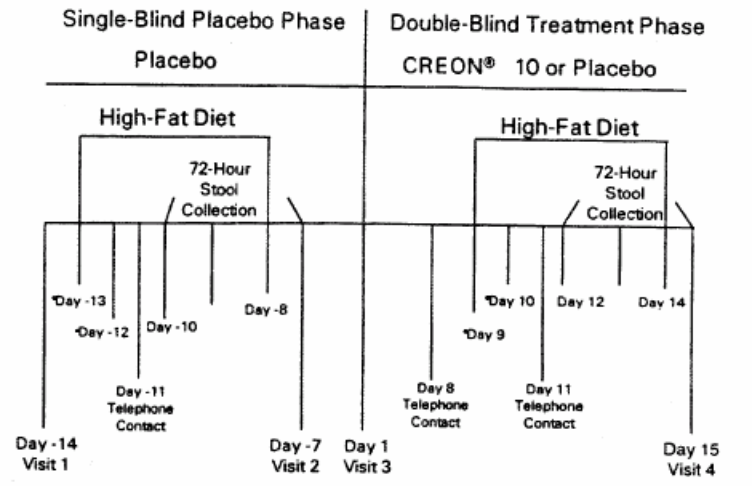
Title: Double blind, randomized, multicenter placebo-controlled, parallel group study of the effects of Creon®10 on steatorrhea in patients with chronic pancreatitis.

Objectives:

Primary: To compare the effect of Creon®10 (10,000 lipase units, USP) with placebo in the control of steatorrhea, as assessed by the coefficient of fat absorption (CFA), in patients with chronic pancreatitis (CP).

Secondary: To investigate the effect of Creon® 10 on stool fat, stool frequency and consistency, and clinical global impression of disease symptoms (CGIDs).
The safety and tolerance of Creon® 10 over a dosing period was assessed.

FIGURE 1.
Study Design



Study design

The study was multicenter, randomized, double-blind and parallel placebo-controlled, 2-arm trial. This study consisted of two consecutive two-week outpatient treatment phases. Patients entered a two-week, single-blind, placebo, run-in-phase in which eligibility (stool fat ≥ 10 g/day and/or CFA < 80%) for the second phase was established. In the second phase, eligible patients were randomized (1:1 distribution) to two weeks of double-blind treatment with either Creon®10 or placebo (Fig 1 scanned, vol. 30, page 5226).

After a pre-study assessment at visit 1 (day –14) patients underwent a 4-day washout period from previous enzyme supplementation and were instructed to begin a high-fat diet (-13 to –8) and a 72-hour stool collection (-10 to –7).

Upon receipt of the stool results, patients who had stool fat values ≥ 10 g/day and/or a CFA < 80% entered into double-blind phase on day 1 (visit 3), where they were randomly assigned (1:1 distribution) to receive a two-week treatment with either Creon® 10 or placebo. Patients who did not meet these criteria were discontinued from further treatment. A final 72-hour stool was collected (day 12 to day 14) at the end of double-blind phase.

During each stool collection period, patients were required to maintain a nutrition diary in which the daily diet was recorded while on a high-fat diet. The fat intake during each collection period was determined from the nutrition diaries by a central dietitian. In addition, patients were required to record on diary cards the number of stools and their consistency each day during stool collection periods. Further, at each scheduled visit, patient and investigator independently evaluated the CGIDS using a 5-point rated scale:
0 = None (symptoms not present)
1 = mild (symptoms present but not bothersome)
2 = moderate (symptoms bothersome)
3 = severe (symptoms interfere with normal activities)
4 = incapacitating (symptoms prevent patients from continuing normal activity)

Inclusion criteria

- Age ≥ 18 years, male or female (females must have negative pregnancy test).
- Clinical history consistent with CP.
- CP confirmed with one of the following: computed- tomography, endoscopic retrograde cholangiopancreatography (ERCP), pancreatic calcification on abdominal x-ray or ultrasound.
- PEI as evidenced by the results of at least one of the following: history of documented steatorrhea, secretin test, serum trypsin, and PABA urinary test.
- Pancreatic enzyme replacement therapy taken for at least six months prior to study entry with satisfactory symptom control. Prior to stool collection, washout period must be at least four days.

Exclusion criteria (pertinent)

- Cystic fibrosis.
- Ileus, acute abdomen, acute pancreatitis within 60 days prior top visit 1, continued abuse of alcohol or drugs.
- Evidence of severe systemic disease.
- Concomitant medication with drugs influencing gastric and duodenal pH (e.g. antacid, antisecretory drugs, anticholinergics, somatostatin), prokinetic agents, agents that alters frequency or consistency of stools (laxatives, iron supplements) or narcotic analgesics. Washout period was 7 days prior to visit 1.
- Partial pancreatectomy with duodenectomy.

Interim exclusion criteria for double-blind phase

- Stool fat < 10 g/day and/or CFA ≥ 80%
- Failure to complete the diaries adequately or non-compliance with dosage regimen

Reviewer's comment: As judged by the inclusion/exclusion criteria, the study population was adequate for the proposed CP study.

Dose selection
During both the single-blind and double-blind phases, patients were instructed to take the study medications orally according to the following dosing regimen: 4 capsules (40,000 lipase units) per meal plus two capsules (20,000 units) per snack. Patients were instructed to take a minimum of 10 and a maximum of 24 capsules daily. Patients who took > 80% of study medication were considered evaluable.

Randomization was generated using SASProc Plan and was done using a block size of 2. Patients were allocated to randomization code numbers in chronological order. Patients were assigned the lowest available number in sequential order.
Reviewer's comment: Randomization scheme was acceptable for the design.

Withdrawal: Development of intolerable AEs, protocol violation, and intercurrent illness. Patient who missed two consecutive visits or non-compliant with study medication.

Statistical method
Analysis of efficacy was performed on the intent-to-treat (ITT) population, which includes all patients who were randomized into double blind phase of the study and took at least one capsule of study drug. All statistical analyses were to be two-sided and were to be considered statistically significant at $p \leq 0.05$. All other statistical analyses on the secondary parameters were for exploratory purposes.

Primary efficacy outcome was defined as the change in CFA from the single-blind phase to double-blind phase. An analysis of variance (ANOVA) with treatment as a fixed factor was performed to test the null hypothesis that the mean change from baseline CFA to the final assessment in Creon® 10 group was equal to that in the placebo group.

Secondary efficacy parameters included stool fat, CGIDs, stool frequency and consistency. These parameters were to be summarized by treatment group comparing change from baseline measurements. The CGIDs were assessed independently by the investigator as well as by the patient.

Safety analysis was to be performed on patients who received at least any one dose of double blind medication and who had data for at least one safety one safety parameter. Safety parameters include adverse events, clinical laboratory parameters, vital sign, concomitant medication, and physical examination.

Sample size: Based on primary efficacy parameter, standard deviation of change from baseline CFA was estimated using baseline to week 4 data from previous study. With 54 evaluable patients (27 per treatment), Type I error of 0.05, standard deviation of 18.23, this study was to have > 80% power to detect a difference of 15 in change from baseline CFA between Creon 10

and placebo**.** Allowing for 20% rate of post-enrollment non-evaluability and attrition (e.g. therapy non-compliance), 68 patients were to be enrolled to ensure 54 evaluable patients.

(b) Results (Vol. 30, page 5267)

Protocol deviation
Protocol deviation occurred in 14 patients, which was evenly distributed between the two treatment groups. The reason for protocol deviation was minor in the majority of cases. However, these patients were included in ITT population for efficacy analysis by the sponsor.

Disposition of patients

64 patients entered in the initial phase of the study, 27 (42%) of who entered double blind phase and completed the study (Table 3). Of the 27 patients entered double-blind phase**,** 13 were randomized to Creon®10 and 14 to placebo. Of 37 patients who were not randomized, 27 did not qualify for entry into the double blind phase (CFA > 80%), and 7 failed inclusion criteria. The first patient was enrolled on Feb 23, 1995 and the last patient completed the study on Nov 2, 1995. **Note:** The sponsor indicated that due to extremely slow enrollment, the study was terminated before reaching the target enrollment of 54 patients for the double-blind phase of the study. The sponsor further reported that this decision was made without unblinding the treatment randomization and analysis of the study. Only 16 of 31 centers were able to recruit patients. The 27 patients were evenly distributed across 16 centers. (scanned, sponsor's Table 7, vol. 30, page 5271)

Sponsor's Table 7. Patient distribution by Investigator

Investigator (Center #)	Placebo (N =14)	CREON® 10 (N = 13)
(b) (6)	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%)

Demographic characteristics of 27 ITT patients are summarized Table 15 (sponsor's Table 8, vol. 30, page 5272).

Table 15. Patient demographics in ITT patients

Characteristics	Placebo (n=14)	Creon®10 (n=13)	p-value
Age (years)			
Mean ± SEM	51 ± 3	51.9 ± 2.7	0.8213
[range]	[31-69]	[38-74]	
Gender			
Female	6 (43%)	3 (23%)	0.4197
Male	8 (57%)	10 (77%)	
Race			
Caucasian	9 (64%)	7(53%)	08383
Negroid	5 (36%)	5 (39%)	
Filipino	0	1 (8%)	

A total of 27 patients, 9 females, 18 males, 16 Caucasian and 10 Negroid between age 31 to 74 years made up the ITT patients. The sponsor stated that there was no statistically significant difference between treatment groups with respect to mean age, proportion of gender or race. The mean age was 51 years in both treatment groups, 57% of placebo patients and 77% of Creon patients were male. Overall, there were more Caucasians than non-Caucasians (16 vs 11, respectively) and more males than females (18 vs 9, respectively).

Drug dosage and duration of exposure

Mean dosage was approximated based on the drug dispensed record. Mean dosage was comparable between Creon®10 and placebo groups receiving 12.5 capsules/day and 14.6 capsules/day, respectively. The mean duration of exposure to Creon® 10 and placebo was 14.6 days and 15 days, respectively. The sponsor presented data on drug dosage and exposure on Appendix 2.5, vol. 31, and individual data are presented in Appendix 5.vol.32 page 6230.

Efficacy

Evaluation of Primary efficacy analysis

The primary efficacy outcome was the change in mean CFA from the end of the single-blind placebo phase to the end of double-bind treatment phase by treatment group. Although the ITT population was 27, the sponsor included 26 patients (14 placebo and 12 Creon 10) in efficacy analysis, one patient #60099 was excluded due to missing data (lost stool collection).

The efficacy results from this study demonstrate statistically significant treatment differences between Creon® 10 and placebo for the primary efficacy parameter (change from baseline CFA), and secondary efficacy parameters (stool frequency, stool consistency) except for CGIDs scores.

The mean CFA values are summarized in Table 16 (sponsor's Table 11, vol. 30, page 5277). As shown in Table 16, the difference between the two treatment groups in the change in mean CFA from the single-blind to the double-blind treatments was statistically significant (p=0.019). Mean CFAs at baseline for the placebo and Creon® 10 treatment groups were comparable during

single-blind placebo-phase (56% and 50%, respectively). After double-blind treatment, the mean CFA for the placebo treatment increased only by 12 percentage point to 68; in contrast, the mean CFA for Creon® 10 treatment increased by 37 percentage points to 87 (p=0.019).

The sponsor performed additional efficacy analysis excluding one patient #60109 whose fat excretion was greater than fat intake during the single-blind placebo-phase. The result showed that the change in mean CFA from the single-blind placebo phase to the double-blind phase between treatments remained significantly different (p=0.023).

Table 16. Summary of CFA in ITT patients (Reviewer's table)

	CFA (%)		p-value[#]
	Placebo group (n=14)	Creon®10 group (n=12)	
Single blind placebo phase			
Mean	55.9	49.9	
Standard Error	3.6	8.8	
[range]	[36-73]	[-33-79]	
Double blind phase			
Mean	68	86.6	
Standard Error	4.6	2.7	
[range]	[40-92]	[67-97]	
Change from single blind to double blind phase			
Mean	12	36.7	0.0185
Standard Error	5	8.7	
[range]	[-22-47]	[1-122]	

p-value was based on ANOVA

Evaluation of Secondary efficacy analysis result

The change in mean fat excretion from single-blind placebo phase to double-blind phase was significantly different between Creon® 10 and placebo groups (p=0.018). There was no apparent difference in fecal fat excretion between placebo and Creon® 10 group during single-blind phase (63 g/day and 75 g/day, respectively). In contrast, there was significantly greater increase (p=0.018) in mean fecal fat excretion in the placebo treated group compared with the Creon® 10 treated group (75 g/day versus 18 g/day). Table 17 summarizes results of fecal fat excretion.

Table 17. Summary of fecal fat excretion in CP patients

	Fecal fat excretion g/day		p-value[#]
	Placebo group (n=14)	Creon®10 group (n=12)	
Single-blind placebo phase			
Mean	63	75	
Standard Error	7.2	18.4	
[range]	[35-130]	[31-260]	
Double-blind phase			
Mean	51.8	18.6	
Standard Error	9.4	4	
[range]	[12-140]	[3-54]	
Change from single-blind to double-blind phase			
Mean	-11.4	-56.5	0.0181
Standard Error	7.1	17.4	
[range]	[-62-40]	[-238 to -4]	

p-value based on ANOVA for H_0: Treatment means are equal with respect to change from the single-blind placebo phase to the double-blind phase

The means and changes in the mean stool frequency for each stool collection period are presented in Table 18.
The change in mean stool frequency from single-blind placebo treatment to double-blind treatment was decreased (-5.6) for patients randomized to Creon® 10 treatment and was essentially unchanged (+0.6) for patients randomized to placebo treatment (p=0.0015). Similarly, there was a significant association detected between the change in stool consistency and treatments (p=0.0102). During the double- blind treatment phase, all 14 patients randomized to placebo reported soft or watery stools. In contrast, 5 of 13 patients randomized to Creon® 10 reported hard or formed stools and 8 reported soft stools, and none reported watery stools.

Table 18. Summary of stool consistency and frequency in ITT patients

	Stool consistency Number (%)		p-value
	Placebo group (n=14)	Creon®10 group (n=13)	
Single blind-placebo phase			
Hard	0	1 (8%)	
Formed/normal	2 (14%)	3 (23%)	
Soft	10 (71%)	6 (46%)	
Watery	2 (14%)	3 (23%)	
Double-blind phase			
Hard	0 (0%)	1 (8%)	
Formed/normal	0 (0%)	4 (31%)	
Soft	13 (92%)	8 (61%)	0.0102#
Watery	1 (7%)	0 (0%)	
	Stool frequency		
Single blind (SB) placebo phase			
Mean ± SEM	14.0 ± 3.6	10.8 ± 2	
[range]	[4-57]	[3-30]	
Double blind (DB) phase			
Mean ± SEM	14.6 ± 4.1	5.2 ± 0.8	
[range]	[3-65]	[2-13]	
Change from SB to DB phase			
Mean ± SEM	0.6 ± 1.0	-5.6 ± 1.5	0.0015@
[range]	[-4-8]	[-17-0]	

p-value based on Fisher's Exact test
@ p-value based on ANOVA

Table 19 Summarizes the CGIDs scores rated independently by investigator and patient. Physician rated the disease symptoms as none or mild in 8 of 13 patients receiving double blind Creon® 10 treatment compared with 4 0f 14 patients receiving placebo treatment in the single blind placebo treatment. In placebo group, 10 of 14 patients had disease symptoms rated by a physician as moderate, severe, or incapacitating during double-blind placebo treatment compared with 7 of 14 patients in a single blind placebo treatment**.** Similar results were noted when CGIDs were rated by patients
No significant association between change in CGIDs and treatment was detected by Fisher Exact test.

Table 19. Summary of CGIDs in ITT patients

CGID scores	Number (%)				p-value#
	Single blind placebo phase		Double blind phase		
	Visit 3		Visit 4		
	Placebo (n=14)	Creon10 (n=13)	Placebo (n=14)	Creon10 (n=13)	
CGIDs scores by Investigator					
None	2 (14)	1 (8)	0	2 (15)	
Mild	5 (36)	3 (23)	4 (29)	6 (45)	0.1020
Moderate	5 (36)	7 (53)	7 (50)	3 (23)	
Severe	1 (7)	2 (15)	2 (14)	1 (8)	
Incapacitating	1 (7)	0	1 (7)	1 (8)	
CGIDs scores by Patient					
None	2 (14)	1 (8)	0	2 (15)	
Mild	3 (21)	3 (23)	2 (14)	6 (46)	0.1272
Moderate	7 (50)	6 (46)	9 (64)	2 (15)	
Severe	1 (7)	3 (23)	2 (14)	2 (15)	
Incapacitating	1 (7)	0	1 (7)	1 (7)	

Fisher's Exact test

Reviewer's comment: The sponsor did not prospectively specify in the protocol as to which statistical methods were to be used to analyze the secondary endpoints. Further, it was indicated that secondary endpoints were for exploratory purposes.

D. Efficacy Conclusions

The sponsor concluded that the data from three controlled studies consistently demonstrated that the Creon® Minimicrospheres® formulation is effective in the treatment of steatorrhea due to EPI associated with CF and CP.

Medical officer comment: The efficacy results in three controlled trials achieved the goal stated in each study protocol, i.e. treatment comparisons were considered statistically significant if $p \leq 5\%$.

The efficacy results from three pivotal trials demonstrated statistically significant treatment differences between Creon® Minimicrospheres® and placebo for the primary efficacy parameter (change from baseline CFA), and all secondary efficacy parameters (stool frequency, stool consistency, CGI in CF studies) except for CGIDs in CP patients.

The primary endpoint measure (change from baseline CFA) chosen by the sponsor appropriately assesses therapy response in patients with steatorrhea due to EPI. In these studies, the proposed drug product achieved a satisfactory response such that the mean CFA increased to 87% from the baseline CFA as low as 50%, which is perhaps the best one can get with most of currently available enzyme replacement therapies. Further, it is worth mentioning that enzyme replacement therapy can hardly ever correct (normalize) fat maldigestion in most patients, particularly in those with substantial degree of malabsorption.

The data from the two CF trials demonstrated substantial evidence ($p<0.001$) to support the efficacy of Creon® 20 in ameliorating symptoms of steatorrhea. Further, the results demonstrated a considerable degree of reproducibility across both studies. Notable in these studies was that adult CF patients required a lower mean daily dose to ameliorate clinical symptomatology than did pediatric and adolescent CF patients (mean Creon® 20 dose 4537 lipase units/kg/day versus 7855 lipase units/kg/day, respectively). However, these CF studies did not involve children under age seven. Pancreatic enzymes are used in infants, toddlers, and preschool-age children with CF. The results from these studies may not be extrapolated to these age groups due to a considerable variation in the standard of care and mode of administration. Appropriate supporting data are required for these age groups.

Even though the efficacy results of Creon® 10 in CP study have achieved the stated goal, the primary efficacy result may not be robust ($p=0.019$) for a single and small study to support the efficacy claim**.** However, in light of the robust and reproducible efficacy results shown across both CF trials, the efficacy claim in CP study could be adequately supported given the close relation of the condition being treated, i.e. steatorrhea due to EPI in both populations. It is worth mentioning that CP is a rare condition with the estimated incidence rate about 5 per 100,000 inhabitants (orphan indication) and about 70% of the patients will develop EPI. Issues regarding one study approach are published in FDA "Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", US department of HHS, FDA, CDER, CBER, May 1998. Further, issues regarding studies in patients with EPI are published in FDA Draft "Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products-Submitting NDAs", US department of HHS, FDA, CDER, March 2003.

It should be noted that in reviewing the efficacy data, this reviewer takes the following issues into account. The efficacy data is based on three randomized clinical studies with a short duration of exposure to the test drug, namely, four weeks in CF studies and two weeks in CP study. Since patients with EPI require a life-long pancreatic enzyme replacement therapy, the quality assurance of the drug product becomes an important factor in assessing the long-term safety and efficacy of the test drug. Due to the inherent lability that has been historically observed with PEPs, a potential inconsistency in drug potency from Batch-to-Batch may exist. As a result, patients may receive a lower or higher dose than intended, a possible safety and efficacy concern. Consequently, the clinical outcome from the trials submitted may not be valid without adequate information in chemistry. The outstanding serious chemistry issues raised by Dr Martin Haber, chemistry reviewer, are the following:

- The applicant did not provided characterization data
- Consistency with respect to chemical identity and biological activity has not been demonstrated.
- The proposed specifications for drug substance (based on the USP monograph) are inadequate.

- More appropriate specifications based on characterization data including tests for identity, biological activity, purity, impurities, and degradants are needed.
- The proposed (b) (4)
- The viral safety evaluation has not yet been completed. The proposed storage is at room temperature, in which the drug substance is markedly unstable at the proposed room temperature.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The integrated safety database contains information from 33 clinical trails involving a total of 1179 patients. Of these, 677 had CF, 299 had CP, 94 had pancreatic surgery (PS) and 109 had diabetes mellitus (DM). These studies were conducted worldwide between July 1985 and November 2000, including the three pivotal trials (2 for CF and 1 for CP) in this NDA submission.

A total of 924 patients received Creon® Microshperes® (Creon MS), 416 patients received Creon® Minimicrospheres® (Creon MMS), 369 received placebo and 311 received other pancreatic enzyme replacement therapy (PERT). (**Note:** Since the majority of studies were crossover designs, patients appearing in the total treatment group were counted several times). The predominant exposure within integrated studies was 2 to 4 weeks. No patient in the Creon MMS group and no patient in the placebo group was treated for more than 26 weeks. The most common daily median lipase dose taken in all treatment groups was in the range of 2,000 to 10,000 U/kg, i.e. 49% with Creon MS, 51% with Creon MMS and 51% with PERT.

The trials completion rate was high in all Creon studies (about 90%). The overall rate of discontinuations due to adverse evens (AEs) was very low and similar in the Creon MMS group (1.9%), in the Creon MS group (1.7%), and in the placebo group (1.6%). The two main AEs that led to withdrawal were body as a whole (1.4%) mainly due to abdominal pain, and the digestive system (1.4%) mainly due to diarrhea and nausea.

Serious advert events (SAEs) including one death were reported in 70 of 1179 patients (6%) (Table 8.8.6.2.1.1, Appendix 3 in this review). The most affected body systems were the body as a whole in 2.5%, respiratory system in 1.7%, digestive system in 1.1%, metabolic and nutritional system as well as cardiovascular system in <1% of patients. The highest incidence rate of SAEs in the Creon group was observed in open, uncontrolled trails with 10% SAEs compared to half of the incidence in controlled trials. The incidence rate of SAEs in controlled trials was comparable among Creon, placebo and other PERT groups. The events reported were predominantly hospitalizations related to the underlying disease state and were considered as not related to the study medication. These complications consisted of conditions such as pneumonia, lung disorder,

pancreatitis and abdominal pain. The one reported death was also related to underlying disease (Narrative under ISS section in this review).

Approximately 65% of all patients experienced at least one treatment emergent adverse event (TESS). The body systems most affected were the body as a whole (43%), digestive system (29%), respiratory system (23%), and metabolic as well as nutritional system (9%). The incidence rates were comparable in the Creon MS and Creon MMS patients (51% each), whereas the other PERT and placebo groups had slightly lower incidence (46% and 42%, respectively) (Table 8.8.8.1.1, Appendix 4 in this review).

> Drug related hyperuricosuria was seen in 5/31 (16%) adult CF patients and 2/34 (5%) pediatric/adolescent CF patients. The increase in urinary uric acid excretion was most likely due to purine content of pancreatic extracts. This laboratory data was from two CF trials in this application and the results are from participants who completed both open-label and double-blind 24-hour urine collections (S2233101, 34 patients; S2233102, 31 patients).

Bases on the reported findings, this reviewer conclude that overall the proposed drug showed an acceptable safety margin with its use in patients with steatorrhea due to EPI associated with CF or CP treated for two to four weeks in the majority of cases. However, since patients with these conditions require life-long enzyme replacement therapy, long-term safety of the study medication cannot be determined from data presented in these randomized clinical studies. The percussion section of the label should include information for physicians to use cautions in patients with gout or renal impairment. **Note:** postmarketing experience has been addressed under appropriate section of this review.

B. Description of Patient Exposure

> Tables 8.8.3.1.1 and 8.8.4.2.1 (scanned, amended vol. 2, pages 491 and 497) summarize data on exposure and daily median lipase dose, and are included as Appendix 1 in this review.
>
> There were 1090 Creon patients with 172 patient years. The Creon MMS group includes 416 patients with an exposure of 29 patient years. The Creon MS group includes 924 patients with an exposure of 143 patient years. The placebo (n=369) group and the other PERT (n=311) group were treated for 26 and 22 patient years, respectively. The patients in the Creon MS group were exposed to study drug about five times longer than the other three groups.
>
> The predominant exposure within the ISS was in the 2- to 4-week interval in which 40% of the total patients received Creon, 68% received MMS, 41% received Creon MS, 29% placebo and 60% received other PERT. The next highest exposure was in the > 4 to 8 week interval (Creon MS 30%, Creon MMS 9%, placebo 8% and other PERT 5%). No patient in the Creon MMS group and

no patient in placebo group was treated for more than 26 weeks in these clinical studies. Thirty patients in Creon MS group were treated for more than one year.

The most common median lipase dose taken in all treatment groups was between 2,000 to 10,000 U/kg/day, for total Creon group in 48%, for Creon MS group in 48%, for Creon MMS group in 51% and for other PERT group in 50% of the patients.

The majority (55%) of patients in CF studies received a median lipase dose between 2,000 to 10,000 U/kg/day in all treatment groups. Only in the CF patient population, the dose category of more than 20,000 lipase U/kg/day was represented. These patients were primarily children and adolescent. The majority of CP patients have also received a median lipase dose between 2,000 to 10,000 U/kg/day, however, no CP patient took > 10,000 lipase/kg/day. Overall, adult patients including CP patients had a lower median total daily lipase dose than CF children.

C. Methods and Specific Findings of Safety Review

The sponsor submitted safety data from 33 clinical studies integrated in the ISS (integrated summary of safety) with cut-off date September 30, 2001. The ISS contains information on patients with CF, CP, pancreatic and gastric surgery and diabetes mellitus (DM). The studies were conducted over an approximate 15 years period in the US, Europe, Australia, New Zeeland and South Africa.

In these studies, different formulations and strengths of Creon MMS as well as Creon MS have been used. All formulations have been combined into the Creon treatment group in the tables for the ISS, as their basic ingredients are the same although the strength, pellet size, and capsule size may differ.

A variety of subgroup analyses have been performed such as patient demographics at entry, drug exposure, median lipase dose, reason for termination, serious adverse events, adverse events leading to withdrawal, treatment emergent adverse events, laboratory data, vital signs and concomitant medications. The sponsor stated that human reproductive data have not been collected and are not applicable to Creon. Further, drug interactions and overdose experience have not been investigated and have not been reported thus far.

Scope of investigations

Table 8.8.1.2.1 Number of patients in ISS Database by design, all Creon studies (n=33)*

Study design	Total patient	Creon MS	Creon MMS	Creon	Placebo	Other PERT
	N	N	N	N	N	N
	1179	924	416	1090	369	311
DB, parallel	300	64	185	229	178	-
DB crossover	496	484	106	484	185	170
Open, crossover	302	296	125	297	-	123
Open, single-treatment	81	80	-	80	6	18

* Since the majority of studies were crossover design, patients appearing in the treatment group "total" were counted several times, i.e. once per treatment. If different Creon formulations were compared in the same study, patients were counted once in the Creon treatment group.

Sponsor's Table 8.8.1.2.1 summarizes study design and all treatment groups.

The ISS compromises information from 33 clinical studies. A total of 1179 patients with steatorrhea due to EPI have been treated. In these studies, 1090 were exposed to Creon with at least one Creon treatment, of which 924 were exposed to Creon MS and 416 to Creon MMS. A total of 369 patients were treated with placebo and 311 patients were treated with other PERT. The majority of patients were treated in crossover, double-blind design studies. These trials were conducted between July 1985 and November 2000.

Demographics

Patient demographics at entry for all Creon studies are summarized in Table 8.8.2.1.1, (scanned, page 489, amended vol. 2), which is Appendix 2 in this review.

A total of 1179 patents participated in the 33 integrated Creon trials. Of these 1179 patients, 677 (54%) patients had CF, 299 (25%) had CP, 94 (8%) were PS patients and 109 (9%) had DM.

A total of 1090 patients were exposed to Creon, of which 924 received Creon MS and 416 received Creon MMS. The majority of the patients receiving Creon were CF patients (62%), 25% were CP patients, 8% were PS patients and 5% were DM patients.

A total of 369 who were treated with placebo include 38 CF patients (10%), 258 CP patients (69%), 19 PS patients (5%) and 54 DM patients (14%). The 311 patients in the other PERT group consist of 277 CF patients (89%) and 34 CP patients (11%).

Overall, a higher number of CF patients have been treated with Creon MS, Creon MMS or other PERT. This is likely because placebo treatment in patients with EPI is difficult to conduct in clinical studies due to severity of the disease, and especially in children with CF. More CP patients were treated with placebo compared to the other diseases.

About 48% of patients were 18 years or younger. This is consistent with the majority of patients being studied were CF patients with a mean age of 13, followed by CP patients with a mean age of 50 years. Overall, thirty patients were < 4 years old, 350 patients were between 4 and 12 years old and 45 patients were 60 years old or older. The majority of patients (65%) were Caucasian and 27% were of unknown race (data not collected). Overall, more males than females were represented in the patient group (59% vs 38%, respectively), gender was not available for 4% of the patients. In CF patients the gender was 51% male, 43% female and unknown in 6%. Whereas in CP patients there were more males than females (70% vs 30%, respectively). Male predominance in CP patients with a higher percentage of alcoholic etiology is representative for this patient group.

The sponsor concluded that the demographic characteristics of the patients enrolled in the 33 integrated studies reflect the natural population of patients with CF and CP. The majority of studies were in CF patients with a mean age of 13 years

Patient disposition and premature termination

Sponsor's Table 8.8.8.5.1.1 summarizes reasons for premature termination,

Table 8.8.8.5.1.1 Reason for termination by treatment all integrated Creon studies (n=33)

			Treatment									
Reason	Total patients		Creon MS		Creon MMS		Creon		Placebo		Other PERT	
	N	%	N	%	N	%	N	%	N	%	N	%
	1179	100	924	100	416	100	1090	100	369	100	311	100
Adverse Event	30	2.5	16	1.7	8	1.9	24	2.2	6	1.6	-	-
Ineffectiveness	2	0.2	1	0.1	-	-	1	0.1	1	0.3	-	-
Intercurrent illness	1	0.1	-	-	-	-	-	-	1	0.3	-	-
Administrative reason	44	3.7	13	104	20	408	33	3	7	1.9	4	1.3
Protocol violation	22	1.9	14	105	2	0.5	16	1.5	4	1.1	2	0.6
Withdrew consent	17	1.4	5	0.5	7	1.7	12	1.1	4	1.1	1	0.3
Lost to follow-up	2	0.2	1	0.1	-	-	1	0.1	1	0.3	-	-
Unknown	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-

Administrative reasons accounted for the majority of the discontinuations, i.e. 3.7% (n=44) in all patients and primarily patients who failed to meet inclusion/exclusion criteria after a run-in-phase.

The rate of discontinuation due to adversers events (AEs) including serious advert events was 2.5% (n=30) in all patients. Withdrawals due to AEs are displayed in sponsor's Table 8.8.7.1.1 (amended vol. 2, page 515). The two main AEs that lead to withdrawal were body as whole (1.4%) mainly due to abdominal pain (0.8%) and the digestive system (1.4%) mainly due to diarrhea and nausea (0.4%). The overall rate of discontinuation due to AEs was very low and similar in the Creon MMS population (1.9%), in the Creon MS population (1.7%) and in the placebo group (1.6%). No patient in the other PERT group withdrew due to an adverse event. In general, the trial completion rate was high in all Creon studies (>90%). The discontinuation rate due to AEs was small and was similar among the individual treatment groups.

Serious adverse events (SAEs)

Deaths

One death was reported in the integrated studies:
Patient 111 (Protocol 223.8.01, Creon MS group, US) was discontinued from the trial due to development of fever, chest pain, productive cough and shortness of breath and died subsequently. This 11.7 years old male with CF had a history of pulmonary complications, Methicillin resistant Staph Aureaus (MRSA) and depression, entered the study on (b) (6), began phase I Creon treatment during the stabilization phase, and was randomized to Creon 25,000 for the first treatment period of the cross over on day 9. The patient was admitted to the hospital with a four-day history of fever, chest pain, and productive cough with some shortness of breath. He developed an allergic reaction. He was placed on I.V. triple antibiotic therapy and respiratory therapy was also administered. MRSA grew from the central line culture and Pseudomonas sp. was isolated from the lung. The patient was discontinued from the study at the end of Phase II

day 20, and was placed on total parenteral nutrition. The patient's condition continued to deteriorate, with increasing oxygen requirements for respiratory distress. Ten days later, the patient suffered cardiorespiratory arrest and died. The physician evaluated the event as not related to the study drug. The reviewer agrees with this evaluation.

Treatment Emergent Serious Adverse Events (SAEs) are summarized in Table 8.8.6.2.1.1 (scanned, amended volume 2, page 503), which is Appendix 3 in this review.

Of a total of 1179 patients, SAEs (including the one death) occurred in 70 patients (5.9%). The most affected body system were the body as a whole with 30 patients (2.5%), the respiratory system with 20 patients (1.7%), digestive system with 8 patients (0.7%), the metabolic and nutritional system with 8 patients (0.7%) and the cardiovascular system in 2 patients (0.2%)

The highest incidence of SAEs in the Creon group was observed in open, uncontrolled trials with up to 20% SAEs. In controlled trial, the incidence of SAEs was lower (4.6%). The sponsor indicated that the incidence of SAEs in the controlled studies was comparable between Creon, placebo and other PERT. The higher overall incidence rate of SAEs for Creon MS comes from open-label studies without an adequate comparator.

Gender analysis for SAEs: In total, 41 patients who experienced SAEs were males and 27 were females; unknown gender for two patients. The only minor difference seen in the gender distribution is in the body as a whole with slightly more male patients (n=6) of all patients experiencing abdominal pain compared to two female patients. In the digestive system, 5 male patients had pancreatitis compared to no female patients. This can be explained by the fact that more male CP patients were randomized into the clinical trials. In the respiratory system, five female patients had pneumonia versus one male patient.

The sponsor stated that the treatment emergent SAEs by race was inconclusive due to the high number of patients whose race was unknown races (n=23) and the comparison of Caucasian (n=38) to the other races with only few patients.

Treatment Emergent Adverse Events (TESS) in all integrated studies

TESS was defined as those events that appeared for the first time during a particular treatment or increased in severity compared to previous treatment.

TESS occurring at a rate ≥ 1% of total patients for all Creon studies is displayed in sponsor's Table 8.8.8.1.1 (scanned, amended vol.2), which is Appendix 4 in this review.

Approximately 65% (n=764) of the 1179 patients experienced at least one TESS. The incidence rates were comparable in the Creon MS patients with 51% compared to 52% in Creon MMS patients. The other PERT has a slightly lower incidence rate with 46% and placebo with 43%. The body systems most affected were the body as a whole (43%), the digestive system (29%), the respiratory system (23%) and metabolic and nutritional system (9%). The body as a whole showed the highest incidence of event in the Creon MMS group (34%) followed by the Creon

MS group (32%) compared to placebo group (27%) and the other PERT group (25%). The sponsor stated that this might be explained by the shorter exposure of patients to placebo and other PERT. In the body system, abdominal pain was the most common event in all treatment groups with the exception of headache in the Creon MMS group.

In the digestive system a total of 342 patients (29%) had treatment emergent adverse events, with diarrhea being the most commonly observed AE (8%). Overall, the incidence rates were comparable between the treatment groups; Creon MS 19%, Creon MMS 19%, other PERT 21% and placebo 18%.

A total of 275 patients (23%) reported TESS in the respiratory system. TESS occurred in 17% in the Creon MS group, 18% in the Creon MMS group, 6% in the placebo group and 14% in other PERT group. Increased cough was the most commonly observed event in all patients (9%) followed by pharyngitis (5%). The sponsor indicated that respiratory events occurred primarily in the active treatment groups, which could reflect the higher number of CF patients in these treatment groups as compared to the placebo group, which was primarily composed of CP patients who would not be expected to suffer from respiratory events.

Intestinal obstruction occurred in two patients, one in Creon MS group and one in other PERT group. Creon MS patient 11, protocol K22.5006, had DIOS, which is commonly found in CF patients (investigator term). The other PERT patient 2, protocol K224.5010 had acute bowel obstruction while receiving Cotazyme-S-Forte.

The overall incidence rates for TESS were slightly lower in the other PERT group and placebo groups compared to the Creon group. However, the sponsor stated that there are no striking differences between the treatments in terms of incidence rates for TESS.

TESS by severity

AEs were characterized as mild, moderate or severe by the investigator. Overall, the majority of TESS in all patients was rated as mild (25%) or moderate (26%) adverse event. Severe TESS occurred in 9% of all patients, (in 6% of the Creon MS group, 5% of the Creon MMS group, 7% of the placebo group and in 3% of other PERT group). Unknown severity was described in 4% of all patients.

In all of the severe TESS, the incidence of abdominal pain was more than 1 % in the placebo group. The sponsor concluded that there was no difference regarding the distribution of severe adverse events between the treatment groups. Overall, TESS was considered unrelated to study drug in 42% of all patients, in 40% of the Creon MMS group, in 32% of the Creon MS group, in 24% of the placebo group, and in 27% of the other PERT group. The relationship to study medication was unknown in 13% of all patients.

In the Creon group, the only TESS that was considered to be related to study medication in > 1% of the patients in the body as a whole was abdominal pain which occurred in 6% and was comparable to placebo with 6%. In the digestive system of the Creon group, diarrhea was

reported as related to study medication in 2%, nausea in 1% and flatulence in 2%, all which was similar in the placebo group. The sponsor concluded that there was no difference in terms of relationship to study medication that could be identified between the treatment groups.

TESS by gender and race:
Overall, TESS occurred in 62% of male patients compared to 68% of female patients. Female patients showed slightly higer incidence of headache, pharingitits and lung disorders compared to males. The sponsor reported that treatment adverse events comparison between Caucasian (n=512, 67%) and other races is difficult due to the higher number of unknown race (n=192, 60%) and the low number of patients of deferent races (3 to 51 patients).

Clinical laboratory parameters
The sponsor stated that the vast majority of laboratory parameters showed no clinically meaningful change from baseline either within or across treatment groups. Laboratory parameters that met the criteria for markedly abnormal were considered to reflect the underlying disease state or condition rather than a treatment effect.

However, a laboratory value of clinical relevance for Creon is urinary uric acid due to the purine content of pancreatin, especially in CF patients. Sponsor's Table 8.8.9.1.1 displays data from urinary uric acid in two pivotal Creon MMS studies (S2233101 and S2233102) conducted in CF patients (trials in this NDA). Study participants who completed both open-label and double-blind 24-hour urine collection were included in the analysis.

The mean change in urinary uric acid from open-label to double-blind phase showed a decrease of 117 mg/24 hrs for placebo group versus a decrease of 26 mg/24 hrs for Creon group (p=0.024). The sponsor stated that this finding supports that hyperuricosuria in patients taking pancreatic enzyme supplements is related to purine content of pancreatic enzyme extracts. In these trials, 5/31 adults and 2/34 children/adolescent had hyperuricosuria (>800 mg/24 hrs) during open-label Creon MMS treatment. During double-blind Creon MMS treatment, 3/31 adults and no child/adolescent had hyperuricosuria. No patients receiving double-blind placebo treatment had hyperuricosuria. The sponsor reported that long-term data on the persistence of hyperuricosurai and its impact on renal function are not available in these studies.

Table 8.8.9.1.1. Urinary Uric Acid (mg/24 hrs) in CF patients

	Open label (OL) Creon treatment		Double blind (DB) treatment		Change fro OL to DB	
	Placebo	Creon	Placebo	Creon	Placebo	CREON
N	32	33	32	33	32	33
Mean	543	563	427	537	-117	-26
p-value					0.024	

D. Adequacy of Safety Testing

Overall, the procedures used to evaluate safety in the submitted ISS are adequate.

E. Summary of Critical Safety Findings and Limitations of Data

The precaution section of the label should inform physician to use cautions in patients with gout or renal impairment due to hyperuricosuria associated with the drug product. The limitation of these data is that long-term safety can not be determined from these clinical studies due to the short-term exposure to the drug product.

VIII. Dosing, Regimen, and Administration Issues

- Pancreatic enzyme dosing in cystic fibrosis is determined by individual body weight and age consistent with the Cystic Fibrosis Foundation Consensus. The dose range as well as the upper limit has been established for patients with CF.

- Dosing in non-CF exocrine pancreatic insufficiency disorders is usually individualized and determined by the degree of maldigestion and malabsorption, the fat content of the diet and the lipase activity of each preparation. Customary clinical practice suggests that a minimum of 30,000 units of lipase should be delivered to the duodenum over a four-hour postprandial interval for adequate digestion of fat. A dose rang or upper dose limit has not been established in non-CF patients.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Even though a subgroup analysis on a small number of study populations may not provide meaningful information, the division statistician, Dr Chen, performed the subgroup analysis by gender. The results did not show any difference between male and female in CF patients. Whereas in CP patients, the efficacy of the drug was superior to that of placebo for male subgroup but not for female, however, there were only three female patients who received the test drug as opposed to 10 male patients in this analysis.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Given the overall small number of patients studied in which half of the patients were randomized to study drug, evaluation of the use of the study drug in special population may not be helpful.

Cystic fibrosis is a very rare disease affecting predominantly white population. In the study submitted, nearly all patients were Caucasian (> 90%), which is representative for the underlying condition. In chronic pancreatitis study the number of patients was small (n=27) and only <10% were older than 65 years.

C. Evaluation of Pediatric Program

The two pivotal studies in CF did not involve children under age seven. Pancreatic enzymes are used in infants, toddlers, and preschool-age children with CF and the proposed labeling includes these age groups. Appropriate supporting data are required for these age groups.

X. Conclusions and Recommendations

A. Conclusions

The sponsor of NDA 20-725 has presented evidence from three pivotal trials, in 101 patients that Creon® Minimicrospheres, delayed-release pancreatic enzyme, is effective in treating steatorrhea due to exocrine pancreatic insuffieciency associated with CF and CP, as assessed by coefficient of fat absorption (CFA), the primary efficacy endpoint.

The efficacy data from three trials revealed that the mean Creon® 20 dose of 7855 lipase units/kg/day in pediatric/adolescent CF patients, 4537 lipase units/kg/day in adult CF patients and the mean number of Creon® 10 capsules, 12.5/day (10,000 lipase units per capsule) in CP patients treated for two to four weeks, significantly increased fat absorption as assessed by CFA.

Further, The efficacy results from these studies demonstrated statistically significant treatment differences between Creon® Minimicrospheres® and placebo for all secondary efficacy parameters (stool frequency, stool consistency, CGI in CF studies) except for CGIDs in CP patients.

The overall safety profile revealed non-serious AEs. The reviewer's assessment of the submitted safety and efficacy of the Creon® Minimicrospheres® shows an acceptable risk benefit.

However, it should be noted that these clinical data may not be valid without adequate information in chemistry.

B. Recommendations

Based on the presented clinical data, I recommend an approvable action for this NDA. The final approval will depend on the resolution of outstanding serious issues in chemistry. The sponsor should adequately address CMC deficiencies.

The two CF studies did not involve children under age seven. The proposed labeling includes age under seven. Appropriate supporting data are required.

The precaution section of the label should inform physicians to use cautions in patients with gout or renal impairment due to hyperuricosuria associated with the drug product.

XI. Appendix

Appendix 1- Drug Exposure and median daily lipase dose

Table 8.8.3.1.1 Exposure - All Integrated Creon Studies (N=33)

Weeks	Creon MS		Creon MMS		Creon		Placebo		Other PERT	
	N	%	N	%	N	%	N	%	N	%
Any	924	100.0	416	100.0	1090	100.0	369	100.0	311	100.0
< 2	160	17.3	59	14.2	164	15.0	190	51.5	87	28.0
2-4	378	40.9	285	68.5	432	39.6	110	29.8	187	60.1
> 4-8	282	30.5	37	8.9	298	27.3	29	7.9	16	5.1
> 8-12	22	2.4	2	0.5	77	7.1	-	-	10	3.2
> 12-26	41	4.4	33	7.9	78	7.2	40	10.8	11	3.5
>26-52	11	1.2	-	-	11	1.0	-	-	-	-
> 52	30	3.2	-	-	30	2.8	-	-	-	-
Sum, days (pat. years)	52314 (143.3)		10601 (29.0)		62915 (172.4)		9463 (25.9)		7995 (21.9)	
mean	56.6		25.5		57.7		25.6		25.7	
median	28		15		28		8		28	

Table 8.8.4.2.1 Median Lipase Dose by Disease State - All Integrated Creon Studies (N=33)

Treatment Group	Disease State	Patients		Median Lipase Dose (U/kg/day)									
				< 2,000		2,000 - 10,000		> 10,000 20,000		> 20,000		Unknown	
		N	%	N	%	N	%	N	%	N	%	N	%
Creon MS	Total	924	100.0	201	21.8	452	48.9	46	5.0	19	2.1	206	22.3
	Cystic Fibrosis	573	100.0	56	9.8	269	46.9	45	7.9	19	3.3	184	32.1
	Chronic Pancreatitis	259	100.0	110	42.5	144	55.6	-	-	-	-	5	1.9
	Post-Surgery	92	100.0	35	38.0	39	42.4	1	1.1	-	-	17	18.5
Creon MMS	Total	416	100.0	64	15.4	216	51.9	23	5.5	-	-	113	27.2
	Cystic Fibrosis	284	100.0	47	16.5	156	54.9	23	8.1	-	-	58	20.4
	Chronic Pancreatitis	53	100.0	14	26.4	39	73.6	-	-	-	-	-	-
	Diabetes mellitus	55	100.0	-	-	-	-	-	--	-	-	55	100.0
	Post-Surgery	24	100.0	3	12.5	21	87.5	-	-	-	-	-	-
Creon	Total	1090	100.0	223	20.5	528	48.4	59	5.4	18	1.7	262	24.0
	Cystic Fibrosis	671	100.0	72	10.7	338	50.4	58	8.6	18	2.7	185	27.6
	Chronic Pancreatitis	272	100.0	118	43.4	149	54.8	-	-	-	-	5	1.8
	Diabetes mellitus	55	100.0	-	-	-	-	-	-	-	-	55	100.0
	Post-Surgery	92	100.0	33	35.9	41	44.6	1	1.1	-	-	17	18.5
Other PERT	Total	311	100.0	55	17.7	158	50.8	14	4.5	3	1.0	81	26.0
	Cystic Fibrosis	277	100.0	32	11.6	147	53.1	14	5.1	3	1.1	81	29.2
	Chronic Pancreatitis	34	100.0	23	67.6	11	32.4	-	-	-	-	-	-

Appendix 2- Patient Demographics

Table 8.8.2.1.1 Patient Demographics at Entry, All Integrated Creon Studies (N=33)

Demographic Category	Treatment									
	Total Patients		Creon MS		Creon MMS		Creon		Placebo		Other PERT	
	N	%	N	%	N	%	N	%	N	%	N	%
All Patients	1179	100.0	924	100.0	416	100.0	1090	100.0	369	100.0	311	100.0
Disease State												
Cystic Fibrosis	677	57.4	573	62.0	284	68.3	671	61.6	38	10.3	277	89.1
Chronic Pancreatitis	299	25.4	259	28.0	53	12.7	272	25.0	258	69.9	34	10.9
Diabetes mellitus	109	9.2	-	-	55	13.2	55	5.0	54	14.6	-	-
Post-Surgery	94	8.0	92	10.0	24	5.8	92	8.4	19	5.1	-	-
Age (yrs)												
< 4	30	2.5	30	3.2	3	0.7	30	2.8	-	-	11	3.5
4-12	350	29.7	327	35.4	131	31.5	347	31.8	6	1.6	154	49.5
> 12-18	184	15.6	151	16.3	87	20.9	181	16.6	16	4.3	66	21.2
> 18-30	110	9.3	69	7.5	55	13.2	107	9.8	23	6.2	41	13.2
> 30-50	265	22.5	182	19.7	81	19.5	228	20.9	169	45.8	12	3.9
> 50-< 65	190	16.1	123	13.3	49	11.8	151	13.9	122	33.1	23	7.4
≥ 65	48	4.1	40	4.3	10	2.4	44	4.0	33	8.9	2	0.6
Unknown	2	0.2	2	0.2	-	-	2	0.2	-	-	2	0.6
Race												
Caucasian	770	65.3	535	57.9	307	73.8	690	63.3	312	84.6	168	54.0
Black	30	2.5	17	1.8	9	2.2	25	2.3	22	6.0	-	-
Oriental	5	0.4	4	0.4	-	-	4	0.4	3	0.8	-	-
Hispanic	3	0.3	3	0.3	1	0.2	3	0.3	2	0.5	-	-
Other*	51	4.3	48	5.2	31	7.5	50	4.6	30	8.1	-	-
Unknown	320	27.1	317	34.3	68	16.3	318	29.2	-	-	143	46.0
Gender												
Male	695	58.9	536	58.0	267	64.2	641	58.8	256	69.4	146	46.9
Female	443	37.6	347	37.6	149	35.8	408	37.4	113	30.6	124	39.9
Unknown	41	3.5	41	4.4	-	-	41	3.8	-	-	41	13.2

* Filipino, South Africa Cape Colored, mixed race

Appendix 3 –Serious Adverse Events

Table 8.8.6.2.1.1 Treatment Emergent Serious Adverse Events – All Integrated Creon Studies (N=33)

COSTART Bodysystem	Preferred Term	Total Patients N	Total Patients %	Creon MS N	Creon MS %	Creon MMS N	Creon MMS %	Creon N	Creon %	Placebo N	Placebo %	Other PERT N	Other PERT %
At Risk		**1179**	**100.0**	**924**	**100.0**	**416**	**100.0**	**1090**	**100.0**	**369**	**100.0**	**311**	**100.0**
Without any SAE		**1106**	**94.1**	**881**	**95.4**	**402**	**96.6**	**1033**	**94.8**	**361**	**97.8**	**306**	**98.4**
Any Body System	**Any SAE**	**70**	**5.9**	**43**	**4.7**	**14**	**3.4**	**57**	**5.2**	**8**	**2.2**	**5**	**1.6**
Body as a Whole	**Body System Total**	**30**	**2.5**	**19**	**2.1**	**5**	**1.2**	**24**	**2.2**	**2**	**0.5**	**4**	**1.3**
	Abdominal Pain	8	0.7	6	0.7	1	0.2	7	0.6	1	0.3	-	-
	Reaction Unevaluable *	5	0.4	4	0.4	-	-	4	0.4	-	-	1	0.3
	Infection	4	0.3	4	0.4	-	-	4	0.4	-	-	-	-
	Reaction Aggravated *	3	0.3	2	0.2	1	0.2	3	0.3	-	-	-	-
	Pain	2	0.2	1	0.1	-	-	1	0.1	-	-	1	0.3
	Flu Syndrome	1	0.1	-	-	-	-	-	-	-	-	1	0.3
	Suicide Attempt	1	0.1	-	-	-	-	-	-	-	-	1	0.3
	Injury / Accident	1	0.1	-	-	-	-	-	-	1	0.3	-	-
	Abdominal Syndr. Acute	1	0.1	-	-	1	0.2	1	0.1	-	-	-	-
	Abscess	1	0.1	-	-	1	0.2	1	0.1	-	-	-	-
	Pain Back	1	0.1	-	-	1	0.2	1	0.1	-	-	-	-
	Cystitis	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
	Fever	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
	Pain Chest	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
Cardiovascular	**Body System Total**	**2**	**0.2**	**-**	**-**	**1**	**0.2**	**1**	**0.1**	**1**	**0.3**	**-**	**-**
	Migraine	1	0.1	-	-	-	-	-	-	1	0.3	-	-
	Tachycardia	1	0.1	-	-	1	0.2	1	0.1	-	-	-	-

* the original terms can be reviewed in Appendix Table 8.8.8.12

** not gender adjusted

Table 8.8.6.2.1.1 (cont.) Treatment Emergent Serious Adverse Events – All Integrated Creon Studies (N=33)

COSTART		Total Patients		Creon MS		Creon MMS		Creon		Placebo		Other PERT	
Digestive	**Body System Total**	**13**	**1.1**	**5**	**0.5**	**4**	**1.0**	**9**	**0.8**	**3**	**0.8**	**1**	**0.3**
	Pancreatitis	5	0.4	2	0.2	-	-	2	0.2	3	0.8	-	-
	GI Disorder	3	0.3	-	-	3	0.7	3	0.3	-	-	-	-
	Obstruction Intestinal	1	0.1	-	-	-	-	-	-	-	-	1	0.3
	Nausea / Vomiting	2	0.2	2	0.2	-	-	2	0.2	-	-	-	-
	Stomach Atony	1	0.1	-	-	1	0.2	1	0.1	-	-	-	-
	Nausea	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
	Vomiting	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
	Pancreas Disorder	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
Metabolic and Nutritional	**Body System Total**	**8**	**0.7**	**5**	**0.5**	**1**	**0.2**	**6**	**0.6**	**2**	**0.5**	**-**	**-**
	Hypoglycemia	3	0.3	2	0.2	-	-	2	0.2	1	0.3	-	-
	Dehydration	2	0.2	2	0.2	-	-	2	0.2	-	-	-	-
	Hypoglycemic Reaction	1	0.1	-	-	-	-	-	-	1	0.3	-	-
	Growth Retard	1	0.1	-	-	1	0.2	1	0.1	-	-	-	-
	Weight Decrease	1	0.1	-	-	1	0.2	1	0.1	-	-	-	-
	Hyerglycemia	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
	Ketosis	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
Nervous	**Body System Total**	**4**	**0.3**	**2**	**0.2**	**2**	**0.5**	**4**	**0.4**	**-**	**-**	**-**	**-**
	Encephalopathy	1	0.1	-	-	1	0.2	1	0.1	-	-	-	-
	Ileus	1	0.1	-	-	1	0.2	1	0.1	-	-	-	-
	Anxiety	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
	Depression	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
	Withdraw Syndrome	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-

* the original terms can be reviewed in Appendix Table 8.8.8.12
** not gender adjusted

Table 8.8.6.2.1.1 (cont.) Treatment Emergent Serious Adverse Events – All Integrated Creon Studies (N=33)

COSTART		Total Patients		Creon MS		Creon MMS		Creon		Placebo		Other PERT	
Respiratory	**Body System Total**	**20**	**1.7**	**16**	**1.7**	**4**	**1.0**	**20**	**1.8**	-	-	-	-
	Lung Disorder	8	0.7	4	0.4	4	1.0	8	0.7	-	-	-	-
	Pneumonia	6	0.5	6	0.7	-	-	6	0.6	-	-	-	-
	Dyspnea	1	0.1	-	-	1	0.2	1	0.1	-	-	-	-
	Asthma	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
	Bronchitis	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
	Hemoptysis	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
	Pharyngitis	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
	Respiratory Disorder	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
	Sinusitis	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-
Urogenital**	**Body System Total**	**2**	**0.2**	**1**	**0.1**	**1**	**0.2**	**2**	**0.2**	-	-	-	-
	Testis Disorder**	1	0.1	-	-	1	0.2	1	0.1	-	-	-	-
	Infect Urin Tract	1	0.1	1	0.1	-	-	1	0.1	-	-	-	-

* the original terms can be reviewed in Appendix Table 8.8.8.12
** not gender adjusted

Appendix 4- Treatment Emergent Adverse Events

Table 8.8.8.1.1 Treatment Emergent AEs (≥1% in total patients) - All Integrated Creon Studies (N=33)

Costart Body System	Preferred Term	Total Patients N	Total Patients %	Creon MS N	Creon MS %	Creon MMS N	Creon MMS %	Creon N	Creon %	Placebo N	Placebo %	Other PERT N	Other PERT %
At Risk		1179	100.0	924	100.0	416	100.0	1090	100.0	369	100.0	311	100.0
Without any AE		415	35.2	452	48.9	201	48.3	484	44.4	212	57.5	167	53.7
Any Body System	Any Adverse Event	764	64.8	472	51.1	215	51.7	606	55.6	157	42.6	144	46.3
Body as a Whole	Body System Total	516	43.8	302	32.7	145	34.9	394	36.2	102	27.6	78	25.1
	Pain Abdominal	213	18.1	117	12.7	46	11.1	152	13.9	42	11.4	36	11.6
	Headache	166	14.1	89	9.6	63	15.1	133	12.2	30	8.1	8	2.6
	Infection	73	6.2	31	3.4	22	5.3	53	4.9	9	2.4	11	3.5
	Fever	65	5.5	38	4.1	13	3.1	49	4.5	4	1.1	12	3.9
	Pain	58	4.9	24	2.6	16	3.9	37	3.4	14	3.8	7	2.3
	Flu Syndrome	35	3.0	14	1.5	9	2.2	23	2.1	10	2.7	3	1.0
	Chills	30	2.5	20	2.2	4	1.0	24	2.2	3	0.8	4	1.3
	Asthenia	25	2.1	6	0.7	9	2.2	15	1.4	8	2.2	3	1.0
	Pain Back	27	2.3	13	1.4	6	1.4	19	1.7	6	1.6	2	0.6
	Reaction Unevaluable*	21	1.8	14	1.5	1	0.2	15	1.4	-	-	8	2.6
	Injury Accidental	16	1.4	6	0.7	4	1.0	9	0.8	7	1.9	1	0.3
	Malaise	17	1.5	8	0.9	3	0.7	11	1.0	2	0.6	4	1.3
	Pain Chest	18	1.5	9	1.0	7	1.7	16	1.5	1	0.3	1	0.3
	Unexpected Benefit*	13	1.1	7	0.8	-	-	7	0.6	-	-	6	1.9
	Reaction aggravated *	13	1.1	7	0.8	4	1.0	11	1.0	-	-	2	0.6
Cardiovascular	Body System Total	17	1.4	5	0.5	4	1.0	9	0.8	7	1.9	1	0.3
Digestive	Body System Total	342	29.0	184	19.9	79	19.0	255	23.4	68	18.4	66	21.2
	Diarrhea	99	8.4	40	4.3	19	4.6	59	5.4	22	6.0	23	7.4
	Vomiting	73	6.2	39	4.2	22	5.3	60	5.5	4	1.1	16	5.1
	Nausea	70	5.9	30	3.3	19	4.6	49	4.5	16	4.3	8	2.6
	Flatulence	56	4.8	28	3.0	12	2.9	40	3.7	18	4.9	6	1.9
	Anorexia	44	3.7	23	2.5	7	1.7	30	2.8	5	1.4	10	3.2
	Constipation	35	3.0	16	1.7	9	2.2	25	2.3	2	0.5	8	2.6
	Dyspepsia	28	2.4	4	0.4	12	2.9	15	1.4	11	3.0	2	0.6
	Stool Abnormality	20	1.7	16	1.7	-	-	16	1.5	-	-	12	3.9
	GI Disorder	19	1.6	4	0.4	8	1.9	12	1.1	4	1.1	3	1.0

*the original term can be reviewed in Appendix Table 8.8.8.12

Table 8.8.8.1.1 (cont.) Treatment Emergent AEs (≥1% in total patients) - All Integrated Creon Studies (N=33)

Costart Body System	Preferred Term	Total Patients N	Total Patients %	Creon MS N	Creon MS %	Creon MMS N	Creon MMS %	Creon N	Creon %	Placebo N	Placebo %	Other PERT N	Other PERT %
Hematic and Lymph	**Body System Total**	**23**	**2.0**	**14**	**1.5**	**2**	**0.5**	**16**	**1.5**	**2**	**0.5**	**6**	**1.9**
Metabolic and Nutritional	**Body System Total**	**111**	**9.4**	**62**	**6.7**	**11**	**2.6**	**71**	**6.5**	**31**	**8.4**	**20**	**6.4**
	Hyperglycemia	29	2.5	18	2.0	1	0.2	19	1.7	8	2.2	4	1.3
	Hypoglycemia	18	1.5	10	1.1	2	0.5	12	1.1	7	1.9	-	-
	Anemia Iron Deficiency	15	1.3	7	0.8	-	-	7	0.6	-	-	8	2.6
	Weight Decrease	14	1.2	11	1.2	1	0.2	11	1.0	2	0.5	1	0.3
Musculoskeletal	**Body System Total**	**24**	**2.0**	**11**	**1.2**	**4**	**1.0**	**15**	**1.4**	**9**	**2.4**	**1**	**0.3**
Nervous	**Body System Total**	**71**	**6.0**	**28**	**3.0**	**17**	**4.1**	**44**	**4.0**	**19**	**5.2**	**9**	**2.9**
	Dizziness	16	1.4	7	0.8	3	0.7	10	0.9	6	1.6	-	-
	Insomnia	12	1.0	2	0.2	2	0.5	4	0.4	4	1.1	4	1.3
Respiratory	**Body System Total**	**275**	**23.3**	**163**	**17.6**	**76**	**18.3**	**224**	**20.6**	**21**	**5.7**	**44**	**14.2**
	Cough Increased	109	9.3	70	7.6	29	7.0	96	8.8	4	1.1	13	4.2
	Pharyngitis	58	4.9	28	3.0	15	3.6	43	3.9	6	1.6	10	3.2
	Lung Disorder	54	4.6	35	3.8	20	4.8	50	4.6	-	-	8	2.6
	Rhinitis	52	4.4	26	2.8	13	3.1	39	3.6	6	1.6	9	2.9
	Bronchitis	26	2.2	13	1.4	6	1.4	19	1.7	3	0.8	4	1.3
	Dyspnea	15	1.3	7	0.8	5	1.2	12	1.1	1	0.3	3	1.0
	Pneumonia	13	1.1	9	1.0	2	0.5	11	1.0	1	0.3	1	0.3
Skin	**Body System Total**	**62**	**5.3**	**32**	**3.5**	**18**	**4.3**	**49**	**4.5**	**12**	**3.3**	**3**	**1.0**
	Rash	29	2.5	17	1.8	9	2.2	26	2.4	4	1.1	-	-
Special Senses	**Body System Total**	**28**	**2.4**	**16**	**1.7**	**8**	**1.9**	**24**	**2.2**	**3**	**0.8**	**1**	**0.3**
Urogenital	**Body System Total**	**33**	**2.8**	**15**	**1.6**	**5**	**1.2**	**20**	**1.8**	**9**	**2.4**	**5**	**1.6**
Urogenital (Females)	**Body System Total**	**16**	**1.4**	**4**	**0.4**	**4**	**1.0**	**8**	**0.7**	**5**	**1.4**	**3**	**1.0**

A. Other Relevant Materials

None

B. Individual More Detailed Study Reviews (If performed)

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

/s/

Fathia Gibril
12/9/03 11:59:01 AM
MEDICAL OFFICER
This is a revised/corrected version (minor), on page 74, second paragraph (section X, subsection B) and page 75, last paragrpgh (subsection B).

Hugo Gallo Torres
12/16/03 08:06:01 AM
MEDICAL OFFICER

Division Director Summary Review of a New Drug Application

NDA: 20-725
Drug: Creon® Minimicrospheres® (pancrealipase delayed-relase capsules, USP)
Applicant: Solvay Pharmaceuticals
Date: October 9, 2003

This new drug application seeks approval of the following indication.

"CREON® MINIMICROSPHERES® Capsules are indicated for adult and pediatric patients with exocrine pancreatic insufficiency as is often associated with, but not limited to:

- cystic fibrosis
- chronic pancreatitis
- postpancreatectomy
- postgastrointestinal bypass surgery (e.g., Billroth II gastroenterostomy)
- ductal obstruction of the pancreas or common bile duct (e.g., from neoplasm)"

Clinical Reviews: As is described in the Medical Officer and Medical Team Leader reviews, the applicant submitted three pivotal trials in support of the application. Two studies were in patients with cystic fibrosis (n=74) and one study was in patients with chronic pancreatitis (n=27). The primary endpoint in all three studies was the effect of treatment on steatorrhea as determined by coefficient fat absorption (CFA) from a 72-hour stool collection.

Both cystic fibrosis (CF) studies were randomized, double-blind, placebo-controlled, multicenter trials utilizing the Creon® 20 Minimicrosphere® capsules (20,000 lipase units, USP). Patients were placed on a high fat diet (≥ 100g fat/day) for the duration of the study. During an open-label 2-3 week run-in period, patients were stabilized on a dose of Creon and a 72-hour stool collection was obtained. Patients with a CFA >80% were randomized to continued Creon or to placebo. After a minimum of 2 days a repeat 72-hour stool fat collection was obtained. The results are shown in Table A in Dr. Gibril's review.

Study S2233101 was conducted in 37 CF patients ages 7-17. During the open label phase the mean CFA was 86% for placebo and 87% for Creon. During the double-blind treatment phase the CFA was 52% for placebo and 84% for Creon. The change from baseline was -34% for placebo and –3% for Creon ($p<0.001$). There was no difference in fat intake between treatment groups in both phases. Secondary endpoints included changes in stool frequency and consistency and physician-rated clinical global improvement (CGI) scores. Creon was superior to placebo in mean stool frequency ($p=0.002$), stool consistency ($p=0.001$), and CGI scores ($p<0.001$).

Study S2233102 was conducted in 36 CF patients ages 18-53. During the open label phase the mean CFA was 88% for placebo and 89% for Creon. During the double-blind

treatment phase the CFA was 51% for placebo and 87% for Creon. The change from baseline was –37% for placebo and –2% for Creon ($p<0.001$). There was no difference in fat intake between treatment groups in both phases. Creon was again superior to placebo for stool frequency ($p<0.001$), stool consistency ($p=0.001$), and CGI scores ($p<0.001$).

Study 223.2.01 was a randomized, double-blind, placebo-controlled, multicenter trial in patients with chronic pancreatitis. Eligibility was established during a single-blind placebo run-in phase. Patients with a 72-hour stool fat ≥10 g/day and/or a CFA value of <80% were eligible for randomization to either Creon 10 Minimicrospheres (10,000 lipase units) or placebo for two weeks. The study randomized 27 patients ages 38-74. The change in mean CFA from the single-blind to the double-blind phases was 12% (from 56% to 68%) for placebo and 37% (from 50% to 87%) for Creon ($p=0.019$). Creon was also superior to placebo for the secondary endpoints of change in mean stool frequency ($p=0.0015$) and change in stool consistency, with more soft stools with placebo ($p=0.010$). However, there were no significant differences in patient or physician CGID scores between the two treatment groups.

The clinical trials database contained safety information from 33 clinical trials. A total of 416 patients received Creon Minimicrospheres and 369 received placebo. Most patients received treatment for 2 to 4 weeks. The most common daily median lipase dose ranged from 2,000 to 10,000 U/kg. In her review of the integrated safety database, Dr. Gibril concluded "… that overall the proposed drug showed an acceptable safety margin with its use in patients with steatorrhea due to EPI associated with CF or CP treated for two to four weeks in the majority of cases. However, since patients with these conditions require life-long enzyme replacement therapy, long-term safety of the study medication cannot be determined from data presented in these randomized clinical studies. The percussion *(sic)* section of the label should include information for physicians to use cautions in patients with gout or renal impairment." The safety of long-term administration was addressed in Dr. Gibril's review of postmarketing experience. The applicant provided reports for the period from October 21, 1982 to September 30, 2001. The most commonly reported AE's included abdominal pain, diarrhea, flatulence, constipation, malabsorption syndrome, nausea, vomiting, rash, urticaria, pruritus, and lack of drug effect. The most common SAE's included intestinal stenosis, intestinal obstruction, stenosis of colon, and colitis. Four deaths were reported but none appeared to be related to Creon. The applicant reviewed the reports where there was histologic evidence of fibrosing colonopathy and noted that all of these patients had received other pancreatic supplements in addition to Creon.

The recommendation of the medical reviewer is that "based on the presented clinical data, I recommend an approvable action for this NDA. The final approval will depend on the resolution of outstanding serious issues in chemistry. The sponsor should adequately address CMC deficiencies. The two CF studies did not involve children under age seven. The proposed labeling includes age under seven. Appropriate supporting data is required." In addition, "the percussion *(sic)* section of the label should inform physicians to use cautions in patients with gout or renal impairment due to hyperurecmia *(sic)*

associated with the drug product." In the medical officer secondary review, Dr. Gallo-Torres concurred that "1. NDA 20-725 is approvable for treatment of steatorrhea due to exocrine pancreatic insufficiency associated with 2 indications: a) cystic fibrosis; and b) chronic pancreatitis… 2. To be approved the sponsor must address and resolve serious Chemistry deficiencies. 3. There are no clinical deficiencies per se, but the sponsor needs to link the intended to be marketed formulation with the formulation used in the clinical trials…"

In a separate review on the issue of the use of mineral oil as a (b) (4), Dr. Gallo-Torres recommends that the product be reformulated with another excipient. 21 CFR 201.302 requires that the labeling of drugs containing mineral oil should contain a warning against the use of such products other than at bedtime and against administration to infants. Since pancreatic enzymes are administered with meals and to some infants with cystic fibrosis the regulation is problematic. The applicant should justify the use of mineral oil or reformulate the product.

Statistical Review: The statistical review by Dr. Wen-Jen Chen concluded that "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." The reviewer noted that "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." Based on the guidance on the characteristics of a single trial necessary to support an effectiveness claim, Dr. Chen concluded that "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." I concur with the medical review team that the two cystic fibrosis studies support the study in chronic pancreatitis. Both indications result in pancreatic insufficiency which is being treated by Creon.

Chemistry Review: The chemistry review by Dr. Martin Haber recommended a "not approvable" action. The basis for this recommendation is as follows:

"The drug substance is an extremely crude natural product material, derived from hog pancreas. There is no characterization data available. Consistency with respect to chemical identity and biological activity has not been demonstrated. The proposed specifications for drug substance (based on the USP monograph) are inadequate. More appropriate specifications based on characterization data and including tests for identity, biological activity, purity, impurities, and degradants are needed. The proposed (b) (4) The viral safety evaluation has not yet been completed. The drug is markedly unstable at room temperature and the proposed storage is at this temperature."

"The drug product has historically been formulated with large stability overages or with only a lower limit on the enzyme activity. The proposed drug product specifications are similar to those proposed for the drug substance and are inadequate with extremely broad proposed acceptance limits. Normally, drug product specifications are proposed based on drug substance specifications. Until adequate drug substance specifications are established, stability testing and expiration dating cannot be established. The drug product is also unstable."

The major chemistry deficiencies are:

1. Drug substance characterization – inadequate, characterization was never done
2. Drug substance reference standards – inadequate, present standards are crude uncharacterized material
3. Drug substance specifications – inadequate, requires specific tests for identity and purity
4. Drug substance viral safety evaluation – inadequate, not completed
5. Drug substance stability – inadequate, stability is poor
6. Drug product specifications – inadequate, requires specific tests
7. Drug product stability – inadequate, cannot be evaluated until tests are established

Specific chemistry deficiencies were communicated to the applicant on June 6, 2003 and on August 20, 2003.

Pharmacology and Toxicology Review: The review by Dr. David Joseph recommended approval with inclusion of statements in the *Carcinogenesis, Mutagenesis, and Impairment of Fertility* section of the labeling to indicate that genetic toxicology studies have not been performed, and that fertility studies in animals have not been performed.

Clinical Pharmacology and Biopharmaceutics Review: The review by Dr. Suliman Al-Fayoumi stated that "from the view point of OCPB, the submission is acceptable provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to the dissolution specifications and language in the package insert."

Division of Scientific Investigations: DSI inspected three study sites. All three received classifications of VAI. DSI's recommendation was that the data from all three sites appeared acceptable for use in drug approval.

EER: The EER's are acceptable.

Advisory Committee: There was no advisory committee meeting for this application.

Conclusion: Although the application is approvable from a clinical standpoint, the chemistry deficiencies warrant a not approvable action. Once the chemistry deficiencies have been addressed, the applicant needs to link the to-be-marketed product to the product used in the clinical trials.

Recommendation: The application should not be approved.

{see appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Robert Justice
10/9/03 06:40:42 PM
MEDICAL OFFICER

Medical Officer Secondary Review of NDA 20-725: Creon® Capsules [Pancrelipase (sometimes referred to as Pancreatin)]

Treatment of Adult and Pediatric Patients with Exocrine Pancreatic Insufficiency

Date Submitted	:	16 December, 2002
Date Completed	:	15 September, 2003
Applicant	:	Solvay Pharmaceuticals Inc. 901 Sawyer Road Marietta, Georgia 30062 Contact person**:** Donald Ruggirello
Pharmacological Category	:	Replacement Therapy for Pancreatic Enzyme Insufficiency
Drug:		
Proprietary Name	:	Creon
Non-proprietary name	:	Pancrelipase (sometimes referred to as Pancreatin)
Chemical Name	:	Pancreatin/Pancrelipase, USP, is a crude mixture of digestive enzymes, principally **lipases** (b) (4) , **proteases (mainly** (b) (4) **and α-amylase,** (b) (4) prepared from hog pancreas tissue
Dosage form	:	Delayed-Release Capsules (enteric coated minimicrospheres) for oral administration
Strength/Potency	:	5000, 10000, or 20000 Lipase units per capsule
Related Documents	:	IND 47,546
Reviewer	:	Hugo E. Gallo-Torres, MD, PhD, PNS Medical Team Leader (GI Drugs) HFD-180

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Clinical Review for NDA 20-725

Executive Summary

I. Recommendations

A. Recommendation on Approvability

NDA 20-725 is **approvable** for the following two indications:
1) steatorrhea due to exocrine pancreatic insufficiency (EPI) associated with **cystic fibrosis.**
2) steatorrhea due to EPI associated with **chronic pancreatitis.**

NOTE: To be approved, the sponsor must address and resolve serious Chemistry deficiencies.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There are no recommendations for Phase 4 studies.

II. Summary of Clinical Finding

EFFICACY

The sponsor of this application (NDA 20-725), Solvay Pharmaceuticals Inc., is requesting approval of the marketing of Creon® Minimicrospheres® for two indications related to exocrine pancreatic insufficiency (EPI): 1) cystic fibrosis (CF) and 2) chronic pancreatitis (CP).
In support of their request, the sponsor submitted data from **three pivotal trials (2 for CF, one for CP)** and two supportive trials (K 245.5005 and K245.5002). The latter were not considered to be adequate to support the sponsor's claim of efficacy and safety of the test medication, for reasons specified in Dr. Fathia Gibril's review. Therefore, these "supportive" studies were reviewed mainly for safety while the 3 pivotal studies were the main focus of the Medical Officer's review by Dr. Gibril. Together, the 3 pivotal trials enrolled a total 101 patients [CF, n = 74 CF; CP, n = 27]. The primary objective of these 3 critical trials was to assess the effect of either Creon®20 (for CF) or Creon®10 (for CP) on fat absorption/excretion, as determined by the **change in the coefficient of fat absorption (CFA).**

CYSTIC FIBROSIS (Table i)

- In support of this indication, 2 well-designed and apparently well-executed placebo-controlled, 2-arm, multi-center, U.S. trials were conducted with Creon® 20 Minimicrospheres® capsules (20,000 lipase units USP). Protocol S2233101 [n=38] was conducted in **pediatric and adolescent** CF patients while the study population in protocol S2233101 [n = 36] consisted of adult CF patients.
- Both CF trials used an adequate and identical multi-center randomized withdrawal design consisting of an initial open-label Creon® 20 run-in-phase at the end of which a 72-h stool collection was performed. The latter, in conjunction to the dietary fat intake, was used to determine the CFA, which in turn served to randomize patients into the next (double-blind) phase. Patients with a CFA > 80% were randomized to receive Creon®20 capsules or placebo treatment during the double-blind phase of the trial. Towards the end of the double-blind phase, the 72-h stool collection was repeated and, taking into consideration the carefully monitored dietary fat intake, determination of the CFA was repeated to be compared to that obtained during the open-label phase.

- A total of 73 eligible patients were randomly assigned to double-blind treatment across both studies: 37 patients received Creon®20 while 36 received placebo (Table i). In protocol S2233101, the mean CFA at the end of double blind treatment for patients receiving Creon®20 treatment was 84% which compared favorably to the 52% seen with placebo-treated patients. As depicted in summary Table i, the change in mean CFA from open-label Creon®20 phase to double-blind was –3% for patients randomized to Creon®20 treatment while it was –34% for those randomized to placebo. This difference between Creon®20 and placebo was both clinically and statistically ($p<0.001$) significant.
- The results in Study Protocol S2233101 were properly replicated in the other well-designed and apparently well-executed clinical trial, Study Protocol S2233102. In the latter the change in mean CFA from open-label Creon®20 phase to double-blind treatment was –2% for patients randomized to Creon®20 treatment vs. –37% for those randomized to placebo. Again, the difference between Creon®20 and placebo was both, clinically and statistically ($p<0.001$) significant.
- It is important to note that dietary fat intake during the double-blind phase did not differ from that seen during open-label phase either study trial. It is therefore reasonable to conclude that the mean difference in CFA between treatment groups is driven from differences in fat excretion while the patients are on a high-fat diet (Table 7 in Dr. Gibril's clinical review). Furthermore, in both pivotal clinical trials the most frequently rated (63 to 89%) stool consistency during open-label Creon® 20 treatment and the double-blind Creon®20 treatment was “formed” stools. In contrast, the majority of placebo-treated patients (78 to 90%) reported “soft” stools during double blind placebo treatment phase. These changes between treatment groups were statistically significant ($p=0.001$).

CHRONIC PANCREATITIS (Table i)

- In support of this indication, one (Study Protocol 223.2.01) double-blind, randomized, parallel-group, placebo-controlled, 2-arm, multi-center U.S. study was conducted with Creon®10 Minimicrospheres® capsules (10,000 lipase units USP). This trial consisted of two consecutive two-week outpatient treatment phases. Patients entered a 2-week, single-blind, placebo run-in-phase in which eligibility for the second 2-week phase was established. Patients who had stool fat value > 10 g/day and who had CFA of < 80% were eligible for double-blind randomization to either Creon®10 or placebo for two weeks.
- Of the 27 randomly assigned to double-blind treatment, 13 patients received Creon®10 Minimicrospheres (MMS) capsules and 14 placebo.
- Refer to Table i. The mean CFA for Creon®10 MMS-treated patients was 87% while for those treated with placebo, it was 68%. The change in mean CFA from single-blind placebo phase to the double blind-phase was -37% for those who were randomized to Creon®10 capsules which compared favorably to the -12% for those patients randomized to placebo. This difference between Creon®10 and placebo is both clinically and statistically (p=0.019) significant. When an additional statistical analysis was performed by excluding one patient whose fat excretion exceeded fat intake during the single-blind placebo phase, the p-value increased to **0.023 but was still statistically significant at the < 0.05 level**. As discussed in detail in Dr. Gibril's review, although clinically and statistically significant the differences between Creon®10 and placebo in the CP trials were not as marked as those seen between Creon®20 and placebo in the two CF trials (see Table i).

Table i
NDA 20-725
Coefficient of fat absorption (CFA) of the three pivotal trials

	CFA (%)						
Protocol #	**Open label (OL) treatment**		**Double blind (DB) treatment**		**Change from OL to DB**		**p-value**
	Placebo [n = 19]	**Creon®20** [n = 18]	**Placebo [n = 19]**	**Creon®20** [n = 18]	**Placebo** [n =19]	**Creon®20** [n =18]	
S2233101	86	87	52	84	-34	-3	**<0.001**
	[n =18]	[n =18]	[n =18]	[n =18]	[n =18]	[n =18]	
S2233102	88	89	51	87	-37	-2	**0.000**
	Single blind (SB) placebo phase		**DB treatment phase**		**Change from SB to DB**		
	Placebo [n =14]	**Creon® 10** [n =12]	**Placebo** [n =14]	**Creon® 10** [n=12]	**Placebo** [n =14]	**Creon® 10** [n =12]	
223.2.01	56	50	68	87	-12	-37	**0.019**

- Analysis of secondary efficacy parameters confirmed that Creon®10 was more effective than placebo in the treatment of CP patients. This applied to the change in mean stool frequency and the change in stool consistency from single-blind placebo treatment to double-blind treatment phase. However, there was no significant difference between treatment groups for clinical global improvement of disease symptoms rated independently by either the investigator or the patient.

- The sponsor concluded that the data from three, adequate and well-controlled studies consistently demonstrated the effectiveness of the Creon® Minimicrospheres® formulation in the treatment of exocrine pancreatic insufficiency in patients with cystic fibrosis and chronic pancreatitis. The efficacy is more convincing for the CF than for the CP indication. However, both the Medical Reviewer and the MTL concur, essentially, with the sponsor's conclusion on efficacy.

SAFETY

The total exposure consisted of a total of 1179 patients with EPI that participated in 33 clinical trials including the 3 pivotal trials submitted in support of the NDA. There were 677 CF patients, 299 CP, 94 post surgical and 109 diabetes mellitus patients. The majority of the clinical trials were crossover designs involving Creon® and another marketed pancreatic enzyme replacement therapy (PERT). A total of 1090 patients were exposed to Creon® (416 to Creon® MMS and 924 to Creon® MS), mostly for 2 to 4 weeks. The median lipase dose was within 2000 to 10000 in the majority of patients.

SAEs, including one death that was unrelated to test medication, occurred in 70 patients (6%). These SAEs were predominantly hospitalizations due to the underlying disease state and not considered related to test medication. Although both the Clinical Reviewer and the MTL agree with the sponsor's conclusion that fibrosing colonopathy has not been reported to occur in patients taking **Creon® alone**, nevertheless, if approved, a Section of the Creon® labeling should refer to the serious adverse event of fibrosing colonopathy that may occur in either CF or CP patients taking orally administered pancreatic enzyme preparations. Another safety finding discussed in Dr. Gibril's review is that of drug-related hyperuricosuria, which was seen in 5/31(16%) adult and 2/34 (5%) pediatric/adolescent CF patients. It was the sponsor's opinion that this AE is related to the **purine content** of pancreatic extracts.

In conclusion, based on the available information, Creon®'s safety profile appears acceptable.

DOSING

The clinical trials utilized two of the three compositionally proportional dose strengths of the drug: Creon®20 (which corresponds to 20,000 USP lipase U) for CF studies, and Creon®10 (which corresponds to 10,000 USP lipase U) for CP studies. Since the patients self-adjusted their medication based on symptoms, it would appear that, in the course of the clinical trials, CF patients were taking higher amounts of enzymes than CP patients, when it should be the other

way around. In addition, the clinical reviewer commented that even though the sponsor adapted the Cystic Fibrosis Foundation Consensus Conference recommendation in the proposed label, this was not prospectively planed in the CF trials submitted in support of the CF indication. In these pivotal trials, the initial dose was not specified. Also, patients were not given guidance about **maximum allowable dose**. These experimental subjects were to adjust their own dose as guided by clinical symptoms. In spite of these constraints, the doses received by patients in both CF trials happened to fall within the recommended dose range, i.e. **500 to 2500 lipase units/kg/meal.**

In the proposed package insert, in the Dosage and Administration selection the sponsor proposes the following:

1) Pancreatic enzyme dosing in cystic fibrosis is to be determined by individual body weight and age consistent with the CFFCC[1]:

- Dose begins with 1000 USP lipase units/kg/meal and for children < four years of age, and 500 USP lipase units/kg/meal for > fours years of age.
- Dosage to be adjusted according to the severity of the disease, control steatorrhea and maintenance of good nutritional status.
- Doses in excess of 2500 USP lipase units/kg/meal should be used with caution and only if they are documented by three-day fecal fat measurements to significantly improve the coefficient of fat absorption.
- Doses in excess of 6000 USP lipase units/kg/meal have been associated with fibrosing colonopathy.

(b) (4)

SPECIAL POPULATIONS

Because the total number of patients who had either CF or CP and were randomized into the pivotal clinical trials was small, assessment of the use of the drug in Special Populations is not very helpful. For example, the total number of patients randomized to test medication in one of the CF studies was 18 pediatric patients, while only 12 adult patients were randomized in the CP trial. It is therefore concluded that assessment of the use of drug in special populations may not provide meaningful information.

[1] Borowitz et al. Use of pancreatic enzyme supplements for patients with CF in the context of fibrosing colonopathy. J. of Pediatric. November (1995)

Clinical Review

I. Introduction and Background

Through NDA 20-725, the sponsor is seeking approval of Creon®, as a replacement therapy for Pancreatic Enzyme Insufficiency (PEI) as is often associated with conditions such as (1) cystic fibrosis (CF), (2) chronic pancreatitis (CP), (3) postpancreatectomy, (4) postgastrointestinal bypass surgery (e.g. subtotal gastric resection with Billroth II anastomosis; Whipple's procedure), and (5) ductal obstruction of the pancreas or common bile duct (e.g. from neoplasm). Of these five, sufficient supporting information for review of the CF and perhaps of the CP indications, has been submitted. Safety and efficacy of the use of Creon® in the treatment of these two primary indications is the main subject of the comprehensive Medical Officer Review by Dr. Fathia Gibril (September 15, 2003). In the current secondary review, only some pertinent information regarding CF and CP is either added or reiterated

- Digestion of macronutrients occurs mostly via enzymatic hydrolysis into small absorbable molecules. In this process, pancreatic enzymes (PEs) play the most important role, although several brush border enzymes and extra-pancreatic enzymes also participate in macronutrient digestion. The crucial importance of pancreatic exocrine function is reflected by the detrimental malabsorption that occurs as a consequence of untreated pancreatic exocrine insufficiency. In addition to the latter, there is a high incidence of biliary tract disease[2] that may be seen in CF patients. In such instance biliary secretion deficiency, further complicating the lumen phase of absorption, may also need to be addressed. However, in both CF and CP patients, other aspects of the intestinal absorption/assimilation process, such as the penetration phase (nutrient uptake), intracellular metabolism, exit from the enterocyte into the lymph or portal vein blood, chylomicron formation and overall systemic nutrient metabolism and utilization, are considered essentially normal.
- Nutrient delivery into the proximal small bowel is the most important stimulus of exocrine pancreatic secretion, and the digestive products, in particular free fatty acids rather than undigested macronutrients, induce cholecystokinin (CKK) release and thereby stimulate enzyme response. As pointed out by many investigators and emphasized by Dr. Gibril, in healthy individuals, 10 to 20-fold more enzymes are secreted by the pancreas that are required to prevent malabsorption. It has been shown in patients with variable degrees of pancreatic insufficiency, that 5 to 10% of normal prandial enzyme output is sufficient to maintain normal net digestion. Enzyme output occurs in concert with intestinal motility both in the postprandial and interdigestive state. These and other data underscore the **importance of individualized treatment**. Modern enteric-coated pancreatic microsphere preparations, such as Creon® attempt

[2] This includes hypoplastic gallbladders, gallstones and/or sludge, common bile duct strictures, common bile duct obstruction from severe pancreatic fibrosis and a cholangiopathy indistinguishable from primary sclerosing cholangitis.

to deliver sufficient enzyme activity into the duodenal lumen simultaneously with meal nutrients by optimizing the size of individual microspheres and chemistry properties of the coating. However, an important concept to keep in mind is that **lipid digestion cannot be completely normalized in most patients by current standard therapy.**

- The three major enzyme groups in the exocrine pancreatic secretion (also found in pancreatic enzyme preparations of biological origin such as Creon®) are: a) lipolytic; b) proteolytic and c) amiololytic for digestion of fats, proteins and carbohydrates respectively. The corresponding enzymes are: a) lipase, (b) (4) ; b) endopeptidases such as (b) (4); and exopeptidases such as (b) (4) and c) amylase.
- As noted in Dr. Gibril's Medical Officer's review, an important issue to consider is the **fate of enzymes during small intestinal transit**. This is controlled by the amount of enzymes released into the duodenum and the survival of enzymatic activity within the intestinal lumen thereby determining the duration during which enzymatic activity is available for digestion during duodenal-ileal transit of chyme. **The rate of intraluminal degradation differs widely among the major enzymes due to different stability against inactivating mechanisms.** Nonparallel disappearance rates of enzymatic activities and immunoreactivities within the same enzymes have been observed[3]. Pathophysiologic mechanisms are summarized in Table 1 [see more on fate of enzymes during small intestinal transit and mechanisms of luminal enzyme degradation under the Biopharmaceutics and Chemistry reviews of NDA 20-725].

Table 1

Earlier and more severe manifestation of fat maldigestion compared to protein or carbohydrate maldigestion: pathophysiologic mechanisms

---

- Earlier impairment of pancreatic lipase synthesis and secretion
- Impaired bicarbonate output leading to more rapid and complete inactivation of lipase in the acidic duodenum
- Further impairment of lipid absorption by bile acid denaturation within the acidic duodenum
- Greater susceptibility of lipase against proteolytic destruction
- Low effectiveness of compensating enzyme systems

From: Layer P and Keller J. Pancreatic Enzymes : Secretion and Luminal Nutrient Digestion in Health and Disease. J Clin Gastroenterol 28: 3-10 (1999)

- It is therefore important to consider which factor may impair enzyme treatment of steatorrhea. These are summarized in Table 2.

NOTE: In addition to the conservative therapeutic options to treat maldigestion/malabsorption as well as diabetes mellitus and abdominal pain, a variety of **endoscopic techniques** are available to treat chronic pancreatitis but very few of these have been subjected to randomized

[3] Layer P et al. Fate of pancreatic enzymes during aboral small intestinal transit in humans. Am J Physiol 251: G475-G480 (1986).

trials. **Surgical therapy** for chronic pancreatitis involves one of three goals: (1) management of intractable pain, (2) treatment of a complication (e.g. pseudocyst or biliary obstruction), or an attempt to distinguish cancer of the pancreas from chronic pancreatitis.

Table 2

Factors impairing enzyme treatment of steatorrhea

- destruction of unprotected lipase by gastric acid
- destruction of substituted lipase by intraluminal proteases
- asynchronous gastric emptying of substituted enzymes and meal nutrients
- delayed liberation of lipase from enteric coated preparations within the intestinal lumen
- accelerated small intestinal transit in pancreatic insufficiency

Source: see footnote to Table 1.

- Important milestones in product development are given in Dr. Gibril's MO Review. It is of interest to reiterate that on July 31, 2001 General Counsel gave final clearance to the Federal Register notice **reclassifying pancreatic enzymes as new drugs** requiring approved new drug applications (NDAs) or abbreviated new drug applications (ANDAs) for continued marketing. A brief summary of the status of available PEI products is given in Table 3.

Table 3

Status of PEI products (based on COMIS information)

DRUG NAME	SPONSOR	STATUS
(b) (4)		Pre-submission status (1993)
Ultrase	Scandipharm	Refuse to file (1994)
(b) (4)		Pre-submission status (1996)
		Pre-submission status (1996)
Cotazym	Organon	**Approved NDA** (1996)
(b) (4)		Not approved NDA (1997)
Ultrase MT	Hellinger, MD	Active IND (1998)
Ultrase	Axcan Scandipharm	Active IND (1999)
Viokase	Axcan Scandipharm	Active IND (2000)
Creon® • **This submission** • **NDA 20-725**	**Solvay**	

- As noted in Dr. Gibril's review, the main diagnostic procedure for cystic fibrosis is the sweat test[4]. For **chronic pancreatitis**, the diagnosis is straightforward in

[4] In which Cl^- concentration is measured in fluid obtained from sweat gland.

patients with far advanced condition; such patients have easily identifiable abnormalities on standard imaging procedures (e.g. calcification on a plain film of the abdomen, calcification and a markedly dilated pancreatic duct on CT, advanced changes on pancreatography).[5] But many patients with chronic pancreatitis do not have these findings, particularly patients with early alcoholic pancreatitis and those with idiopathic chronic pancreatitis[6]. This distinction has led to a general characterization of patients: those having substantial abnormalities of pancreatic structure such as calcification and a dilated pancreatic duct (**'big duct disease"**) and those lacking these changes **("small duct disease"**). This distinction has both **diagnostic and therapeutic implications.** This is because in patients with "small duct" disease, not only is diagnosis much more difficult, but the treatment options are also different (**particularly with regard to the treatment of pain**)

- For evaluation of EPI due to CF or PI, direct and indirect tests, described in Dr. Gibril's review, are used. Tests of pancreatic exocrine function include secretion with/without CCK: decreased [HCO_3^-], decreased enzyme output; tripeptide test (bentiromide): decreased urine excretion of PABA; decreased serum trypsinogen, decreased serum pancreatic isoamylase; and other indirect pancreatic function tests. These tests are frequently necessary to establish the diagnosis because only one fifth of patients with pancreatic exocrine insufficiency have the classic diagnostic triad. Diagnostic tests for chronic pancreatitis are listed in Table 4. Note that although widely used, including in the Creon® clinical trials in chronic pancreatitis patients, ***fecal fat is not a very sensitive test.***

Table 4
Diagnostic Tests for Chronic Pancreatitis
Listed in Order of Decreasing Sensitivity

FUNCTION	STRUCTURE
Secretin or secretin/CCK test	Endoscopic retrograde pancreatography
Bentiromide test	Computer tomography scan
Serum trypsinogen	Magnetic resonance imaging
Fecal elastase	Ultrasonography
Fecal chymotrypsin	Plain abdominal radiography
Dual-label Schilling test	
Fecal fat	
Blood glucose	

Source: Toskes PP. Update on Diagnosis and Management of Chronic Pancreatitis. Current Gastroenterology Reports
1: 145-153 (1999)

[5] Forsmark CE, Toskes PP. What does an abnormal pancreatogram mean? Gastrointest Endosc Clin North Am 5: 105-123 (1995)
[6] Layer P et al. The different courses of early and late-onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology 107: 1481-1487 (1994)

- The most frequently employed test is the **72-hour fecal fat excretion.** Malabsorption is diagnosed when fecal fat excretion exceeds 7% of the dietary fat ingested (15% for infants < 6 months of age). In addition to establishing the presence of EPI, this tool can also be used to assess the treatment responses.
- The clinical trial in CF and CP patients in NDA 20-725 used the **Coefficient of Fat Absorption (CFA) as the primary efficacy parameter.**

NOTE: Because the CFA is a test, a search for the origin and supportive data regarding the characteristics of such a test (sensitivity, specificity, positive and negative predicted value) was undertaken. But no studies on the characteristics of this experimental and clinical tool per se seem available. There is no doubt that the CFA is a **standard technique.** Based on the limited available information, one can guess it goes back into the 19th century. In a paper by Morgan and Hofmann[7] the authors referred to an old Bockus book, chapter by M. Kalser[8]. Frazer in his book[9] refers to a paper by Cooke et al[10] published just after the war.
Schoenheimer used the balance technique in 1936[11] It seems that the **accepted upper limit of normal of 7 g/day** goes back to Wollaeger and his co-workers from the Mayo Clinic. According to the many publications by many authors who did work at the Mayo Clinic, this institution always did a 3-day stool collection on a defined **100 g fat intake**. Pertinent publications by Wollaeger are given as a footnote[12].

- Is there a technique other than CFA? Yes. In McCollum's book on "A History of Nutrition" he has a chapter on ***calorimetry.*** Gruy-Kapral et al (one of the co-authors of this publication is Alan Hofmann) published a paper in which bomb calorimetry was done on a patient with malabsorption in whom the effect of exogenous conjugated bile acids was tested[13]. In balance studies, conjugated bile acid replacement therapy caused fat absorption to increase by ca. 40g. They concluded that conjugated bile acid replacement therapy should be part of the armamentarium for the treatment of selected patients with the short bowel syndrome. But, to date, the characteristics of calorimetry as a diagnostic and follow-up treatment test have not been described.
- As pointed out in Dr. Gibril's review, in NDA 20-725, the CFA was calculated from 72-h stool values and fat intake data from nutritional diaries. The primary

[7] Morgan RGH and Hofmann A: Use of ^{3}H-labeled triether, a nonabsorbable oil-phase marker, to estimate fat absorption in rats with cholestyramine-induced steatorrhea. J Lipid Res 11: 231-236 (1970)
[8] Kalser M. *In* Gastroenterology. H L Bockus, editor. W B Saunders Company, Philadelphia, Pa. 2nd edition. 2: 492 (1964)
[9] Frazer A C. Malabsorption Syndromes, William Heinemann Medical Books Limited, London (1968)
[10] Cooke W T et al. *Quart J Med* 15: 141 (1946)
[11] Shapiro A, Koster H, Rittenberg D and Schenheimer R. The origin of fecal fat in the absence of bile, studied with deuterium as an indicator. J Biol Chem 116: 525-528 (1936)
[12] Wollaeger E E et al. FECAL AND PLASMA LIPIDS. A Study of 2 Normal Human Adults Taking (1) A Diet Free of Lipid and (2) A Diet Containing Triolein as the Only Lipid. Gastroenterology 24: 422-436 (1953)
Wollaeger E E . Editorial: Fat, feces , and the importance of the ileum. Mayo Clinic Proc 48: 833-835 (1973)
[13] Gruy-Kapral C et al. Conjugated Bile Acid Replacement Therapy for Short Bowel Syndrome. Gastroenterology 116: 15-21 (1999)

efficacy measure was change from baseline (open label) to final (double blind) assessment in the CFA. A total of two 72-h stool collections were scheduled. The secondary efficacy parameters measured the change from open label Creon20 treatment to double-blind treatment for number of bowel movements as well as most frequent stool consistency per stool collection period, and clinical global improvement (CGI). These approaches are all appropriate.

- There is a DRAFT Guidance for Industry for orally administered Exocrine Pancreatic Insufficiency Drug Products. Although **not binding**, this guidance is nevertheless useful in assessing NDA components for this type of product. In essence, the applicant is expected to include six months L-T stability data (ICH) and three months accelerated stability data (also ICH); additional stability data may be submitted as an amendment during the review process and an expiration date will be determined based on the FDA review of the data submitted. The issue of overage is still under discussion. For delayed-released capsules, like Creon®, the dissolution method provided in the monograph in USP 24, page 1259 would be adequate (some modifications to this monograph, if justified, might also be adequate). Also described in the Draft Guidance for Industry are the requirements for Sections on Non-clinical Pharmacology and Toxicology, Human PK and Bioavailability, and Clinical Data. In essence, for drugs under (Section 505(b)1), as in the case of Creon®, the effectiveness of safety of the new drug should be demonstrated by **adequate-and-well-controlled studies**. Because these drugs are to be taken on life long bases, appropriate L-T safety studies should be constructed to address chronic uses of these medicines. The one approved pancreatic extract drug product [Cotazym, an immediate release product from Organon] is not currently marketed. In compliance with FR notice, Solvay Pharmaceuticals Inc. submitted an NDA for a PEP, Creon® 5, 10, and 20 capsules in July 31, 1997. The NDA, 20-725, was resubmitted on December 16, 2002.
- In the current **secondary review** of NDA 20-725, reviews from all pertinent disciplines, primarily the Clinical Review by Dr. F. Gibril, are considered. Based on this multidisciplinary approach, an overall recommendation for regulatory action is formulated.
- **NOTE:** Additional pertinent information, such as drug product history, is found in Dr. Gibril's Clinical review.
- The proposed trade name is Creon®, the non-proprietary name is pancrelipase (sometimes referred as pancreatin, USP) and the product consists of a crude mixture of digestive enzymes, principally lipases, proteases, and α-amylase, prepared from hog pancreas tissue (b) (4)
- The proposed enzyme USP units per capsule are given in Table 5.

Table 5
CREON ® Minimicrospheres ®
(Pancrelipase, Delayed-Release Capsules, USP)

	Creon 5 (USP units/capsule)	**Creon 10** (USP units/capsule)	**Creon 20** (USP units/capsule)
Lipase	5,000	10,000	20,000
Amylase	16,600	33,200	66,400
Protease	18,750	37,500	75,000

These three drug products are currently marketed. According to the firm, Creon 5, 10, and 20 capsules have the same formulation, enteric coating, and process technology for the Minimicrospheres as Creon capsules, the original enteric-coated Creon product containing 80000 USP units of lipase. All three products are manufactured by Kalie-Chemie Pharma in Germany.

- The proposed primary and secondary indications for Creon® Minimicrospheres® capsules for adult and pediatric patients with exocrine pancreatic insufficiency are:

1. **Cystic fibrosis**
2. **Chronic pancreatitis**

3. Postpancreatectomy
4. Postgastrointestinal bypass surgery (e.g. Billroth II gastroenterostomy)
5. Ductal obstruction of the pancreas or common bile duct (e.g. from neoplasm)

- Regarding dosage and administration, the sponsor states that clinical experience should dictate initial starting dose. Dose should be taken during meals or snacks, or as prescribed by a physician. The number of capsules or capsule strength given with meals or snacks should be estimated by assessing which dose minimizes steatorrhea and maintains good nutritional status.
- The directions for dosing in cystic fibrosis according to the CFF Consensus Conference published in November 1995 are listed in Dr. Gibril's review. In short, weight-based enzyme dosing **should begin with 1,000 USP lipase units/kg/meal** for children < four years of age and with **500 USP lipase units/kg/meal** for those over age four. Dosage should be adjusted according to the severity of the disease, control of steatorrhea and maintenance of good nutritional status. Dosage **in excess of** a) **2,500 USP** lipase units/kg/meal should be used with caution and only if they are documented by three-day fecal fat measurements to significantly improve the coefficient of fat absorption and b) **6,000 USP** lipase units/kg/meal have been associated with **fibrosing colonopathy** [more on fibrosing colonopathy under SAFETY].
- Dosing in other exocrine pancreatic insufficiency disorders should be individualized and determined by the degree of maldigestion and malabsorption, the fat content of the diet and lipase activity of each preparation. The usual initial dosage for Creon Minimicrospheres capsules is 10,000 to 20,000 lipase units per meal or snack. The number of capsules or capsule strength given with meals or snacks should be estimated by assessing which dose minimizes steatorrhea and maintains good nutritional status. In the controlled trials in CP patients, 40,000 lipase units with meals (3 main meals per day) and 20,000 lipase units with snacks (2 snacks per day) were administered to improve fat absorption. It is stated that customary clinical practice suggests that a minimum of 30,000 units of lipase should be delivered to the duodenum over a 4-h post-prandial interval for the adequate digestion of fats.

- Please see Dr. Gibril's Clinical review for issues such as State of Armamentarium for Indication(s), Important Milestones in Product Development, Other Relevant Information and Important Issues with Pharmacologically Related Agents. It is to be noted that, other than the potential to induce fibrosing colonopathy, there are no important issues with pharmacologically related agents.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. CHEMISTRY

- Dr. Martin Haber, the Chemistry reviewer's recommendations and conclusions on approvability are: **not approvable** [Chemistry review of August 19, 2003].
- Dr. Martin provided the following description of the Product(s) and Drug Substance (s). The drug substance is a **very crude mixture of digestive enzymes**, principally l**ipases** (pancreatic lipases, (b) (4)), **proteases** (mainly (b) (4)) and **α-amylase.** It is prepared by **Scientific Protein laboratories,** Waunakee, WI (Type II DMF 9649 holder) (b) (4). Dr. Haber stated that **the enzymes of the drug substance are not well characterized or controlled.** The drug substance is stored at room temperature and is also **very unstable.**
- (b) (4)
- The drug product capsules contain delayed-release **"minimicrospheres"** or about (b) (4) diameter particles of the enzyme mixture that are enteric coated with hypromellose phthalate, PEG, mineral oil, dibutyl phthalate and dimethicone to protect them from gastric acid. The enteric coating is designed to break down at higher pH (above 6) in the duodenum and release the active enzymes. All three strengths of hard gelatin capsule contain identical minimicrospheres and the active strength of the capsule is determined by the amount of minimicrospheres that it contains with a larger capsule size containing more minimicrospheres. Drug product capsules are manufactured by Solvay Pharmaceuticals Gmbh, in Neustadt, Germany. Dr. Haber concluded that **the chemical manufacturing and controls for the drug product capsules are deficient.**
- Dr. Haber noted that some clinical trials were conducted with a different formulation containing a different, larger, "microsphere" formulation contained the same active and inactive components in different amounts. Other strengths (e.g., 8000, 12000, or 25000 Lipase units/capsule) were also used in some supportive clinical studies.
- A description by Dr. Haber of how the drug product is intended to be used follows. The usual initial starting dose is 10000 to 20000 lipase units per meal. Doses are taken during meals in

order to aid digestion. The draft labeling recommends (b) (4) **The maximum daily dose is unclear.** Dr. Haber explains that the proposed expiration dating period is (b) (4) but this is not supported by stability data since the product is unstable. The recommended storage condition is controlled room temperature.

- Dr. Haber, the Chemistry reviewer, provided the following basis for his **Not-approval recommendation.** He reiterated that the drug substance is an extremely crude natural product material derived from hog pancreas. There is no characterization data available. Consistency with respect to chemical identity and biological activity has not been demonstrated. The proposed specifications for drug substance (based on the USP monograph) are inadequate. More appropriate specifications based on characterization data and including tests for identity, biological activity, purity, impurities, and degradants are needed. According to Dr. Haber, the proposed use of (b) (4) He further notes that the viral safety evaluation has not been completed. He reiterates that the drug substance is markedly unstable at room temperature but, in spite of this, the proposed storage is at this temperature.
- In addition, Dr. Haber comments that the drug product has historically been formulated with **large stability overages** or with only a **lower limit on the enzyme activity**. The proposed drug product specifications are similar to those proposed for the drug substance and are inadequate with **extremely broad proposed acceptance limits**. Customarily, drug product specifications are proposed based on drug substance specifications. **Until adequate drug substance specifications are established, drug product specifications cannot be finalized.** Until the drug product specifications are established, stability testing and expiration dating cannot be established. He notes, once again, that **the drug product is also unstable.**
- The record indicates that an initial filing review and IR letter with several chemistry deficiencies was issued on 06/06/03. The firm provided very preliminary responses in the 07/09/03 and 08/08/03 Amendments.
- Dr. Haber concludes that the NDA remained **not approvable from a chemistry viewpoint**. **Major deficiencies** are:

		REASONS FOR INADEQUACY
1.	**Drug Substance** Characterization	- characterization was never done
2.	Drug Substance Reference Standards	- present standards are crude uncharacterized material
3.	Drug Substance Specifications	- requires specific tests for identity and purity
4.	Drug Substance Viral Safety Evaluation	- not completed
5.	Drug Substance Stability	- stability is poor
6.	**Drug Product** Specifications	- requires specific tests
7.	Drug Product Stability	- cannot be evaluated until tests are established

B. ANIMAL PHARMACOLOGY and TOXICOLOGY

Included below are excerpts from Dr. David Joseph's overall conclusions and recommendations (review dated September 4, 2003).

- Dr. Joseph d that the formulation is designed to resist inactivation of the enzyme preparation that would occur in the acidic environment of the stomach, prior to delivery into the duodenum and that the protection of enzymes from destruction in the gastric medium is especially important for lipase, which is the most sensitive to low pH among the pancreatic enzymes.
- The maximum total daily dose can be estimated based on an assumed daily ingestion of 60 Creon® 20 capsules a 60-kg adult (equivalent to 20 capsules in a 20-kg child). Ingestion of 60 Creon® 20 capsules daily would result in a daily dose of 20,000 USP Lipase units/kg/day (equivalent to 300 mg/kg/day pancreatin, based on Sponsor's information), which is equal to the maximum recommended dose of 6000 USP Lipase units/kg with each of three meals, plus 2000 USP Lipase units/kg with snacks.
- The Sponsor submitted the following pre-clinical studies of the drug substance: gastrointestinal motility study in mice, 1-month oral toxicity study in dogs, 9-month oral toxicity study in dogs. Pre-clinical studies of the drug product included two pharmacology studies in minipigs with exocrine pancreatic insufficiency (EPI), and a PK study in pigs with EPI.
- The pharmacological activity of the drug product was demonstrated in two studies using the **minipig** model of EPI. In one study, Creon® 10,000 mms (minimicrospheres) produced a dose-dependent improvement in the digestibility of fat and dry matter in pancreatic duct-ligated minipigs. In the other, Kreon® 10,000 mms (same product as Creon®) produced a dose-dependent increase in the digestibility of fat, protein, and starch in the same model of EPI. The increase in daily fecal output was partially reversed by Kreon® 10,000 mms.
- The drug substance had no effect on gastrointestinal charcoal propulsion in mice at a dose of 1500 mg/kg p.o., the only dose tested. A PK study demonstrated the lack of absorption of pancreatic lipase, procolipase/colipase, and trypsin after oral administration of Creon® 10,000 mms in pancreatic duct-ligated pigs or in pancreatectomized pigs.
- A 4-week oral toxicity study of pancrelipase in Beagle dogs was performed using dose levels of 0 (placebo), 1000, 3000, or 6000 mg/kg/day (pancreatin powder in capsules). An additional group was treated with 6000 mg/kg/day pancreatin pellets in capsules[14]**.** Four males and four females were assigned to each group, and dosing was performed twice daily. The pancrelipase dose levels were equal to 94,460, 283,380, and 566,760 FIP Lipase units /kg /day for the groups treated with the powder formulation, and 321,924 Lipase/kg/day for the group treated with the pellet formulation. **A NOAEL was not established.** Oral administration of 1000, 3000, 6000 (powder), and 6000 (pellets) mg/kg/day produced glandular dilatation in the small intestine. Thyroid concretions occurred in the 6000 mg/kg/day pellets group.
- A 9-month oral toxicity study of pancrelipase in Beagle dogs was performed using dose levels of 0 (placebo), 1000, 2000, or 4000 mg/kg/day (4 dogs/sex/group). Dosing was

[14] Pancreatin is a powder concentrate of pancreatic enzymes that is essentially the same as **pancrelipase**, the drug substance in Creon® Minimicrospheres®. For most experiments, especially those in dogs, it is assumed that the test article was actually pancrelipase, but was referred to as pancreatin by the authors.

performed twice daily. The pancrelipase dose levels were equal to 98,700; 197,400; and 394,800 FIP Lipase units/kg/day. Liver was a target organ of toxicity in the 4000 mg/kg/day group, as indicated by an increased incidence and severity of fat accumulation. The authors postulate that the effect in liver may have been the consequence of nutritional and/or metabolic imbalances, as food consumption was reduced in the 4000 mg/kg/day group. The authors attributed the decreased food consumption to the high caloric value of the test article at the given dose level. Despite the signs of reduced food consumption at the 2000 and 4000 mg/kg/day dose levels, weight gain was increased by 43 to 78% in all treatment groups, except for the 1000 mg/kg/day males. This weight gain was not due to overt peripheral fluid retention (edema). Treatment with 1000, 2000, and 4000 mg/kg/day produced a low incidence of hemorrhage in large intestine. Concretions and cysts in thyroids were observed in all drug-treated groups.

- Dr. Joseph noted that the submitted toxicity studies of pancrelipase provide useful safety information with relevance to the drug substance. However, the clinical use of the drug product may require the ingestion of a large number of capsules, which would result in the intake of high dose levels of certain **excipients.** The Sponsor estimates that as much as 60 Creon® 20 capsules will be ingested daily in a 60-kg patient, based on a maximum recommended dose of 6000 Lipase units/kg/meal. Therefore, any adverse effect that is associated with the clinical use of the drug product may be caused by the drug substance, one or more of the excipients, or an interaction between the drug substance and the excipients. Thus, the information provided by the 1-month and 9-month oral toxicity studies of pancrelipase in dogs is of limited value in the evaluation of the potential toxicity associated with the drug product. Clearly, the results of these studies would have been more relevant to the potential human toxicity if the drug product had been used.
- Regarding excipients, Dr. Joseph noted that, on request from HFD-180, the Sponsor previously submitted PK and toxicology studies on the major excipients present in Creon® Minimicrospheres®[15].The pre-clinical studies of excipients included information on hydroxypropylmethylcellulose phthalate, dibutyl phthalate, dimethicone 1000, polyethylene glycol 4000, and light mineral oil. In some cases, the information consisted of summaries of ADME or toxicology studies, with few details provided.
- As addressed in Dr. Joseph's review, PK studies of **hydroxypropylmethylcellulose phthalate** (HPMCP) were performed in rats. HPMCP was poorly absorbed following oral administration[16]. Phthalic acid was identified as a major metabolite excreted in urine. The proportion of unchanged drug and phthalic acid in urine was not stated. **All of the radioactivity in feces was associated with unchanged drug.** Following oral administration of [^{14}C]HPMCP, approximately 93% of the total radioactivity was excreted in feces at 72 h post-dose. Excretion in urine accounted for about 1% of the total radioactivity.
- Oral administration of up to 15,000 mg/kg HPMCP produced no deaths in rats. Oral toxicity studies of one month (1300, 2000, 3000, 4500, and 10,000 mg/kg/day) and six months (1500, 3000, and 6000 mg/kg/day) duration in rats were submitted. The NOAEL was 4500

[15] **These studies were reviewed in the Pharmacologist's Review of IND 47,546** dated May 23, 1997, and were also submitted in the present application.

[16] **Most of the radioactive dose was present in the gastrointestinal contents at 6 h after oral administration of [^{14}C]HPMCP (93.3% in males, 81.5% in females).**

mg/kg/day in the 1-month study. **No target organs of toxicity were identified.** All animals in the 10,000 mg/kg/day group and the vehicle control group (1.5 % sodium bicarbonate, same dose volume) died between days 10 to 16. Dr. Joseph reasons that **the deaths in the high-dose group may have been related to the vehicle.** The NOAEL in the 6-month rat study was 6000 mg/kg/day. **Target organ toxicity was not observed.** [NOTE: based on Dr. Joseph' evaluations, these studies are of **limited usefulness in assessing the toxicity of HPMCP.** Reasons include the small number of organs examined in each study and the fact that **no segment of the gastrointestinal tract was examined** in these studies].

- **Dibutyl phthalate** was rapidly absorbed in rats and hamsters after oral administration. Radioactivity was distributed throughout the body following oral administration of [^{14}C]dibutyl phthalate in rats. At 48 h after administration, no organ contained more than 0.7% of the radioactive dose. When rats were given a diet containing 0.1% dibutyl phthalate for up to 12 weeks, there was no accumulation in any organ that was studied. Metabolism of dibutyl phthalate was demonstrated in rat liver homogenate, and intestinal mucosal cell homogenates from rat, ferret, and baboon. The metabolites included phthalic acid, monobutyl phthalate glucuronide, 3-keto-butyl-phthalate, and 4-carboxypropyl phthalate. Following oral administration of [^{14}C]dibutyl phthalate in rats, 85-100% of the dose was excreted in urine at 24 h post-dose. Urinary excretion accounted for 79% of the dose following oral administration in hamsters.
- Brief summaries of the following toxicity studies of dibutyl phthalate were submitted: 6-week oral study in rats, 80-day oral study in rats and mice, 3-month oral study in rats, 6-month oral study in rats, two 1-year dietary studies in rats, and a 1½-year oral study in rats. The oral no effect doses were the following: 1000 mg/kg/day in the 6-week rat study (only dose tested), 120 mg/kg/day in the 3-month rat study, 2.5 mg/kg/day in the 6-month rat study (only dose tested), 75 mg/kg/day in a 1-year dietary study in rats (only dose tested), 150 mg/kg/day in a 1-year dietary study in rats, and 1000 mg/kg/day in the 1½-year rat study (only dose tested). **A high incidence of deaths occurred at 750 mg/kg/day in a 1-year dietary study in rats.** Death also occurred in rats treated orally with 1200 mg/kg/day in the 3-month study. Because no details of the study methods were provided for the toxicity studies, it is difficult to assess the quality of these studies.
- A brief summary of a **teratogenicity (Segment II)** study of dibutyl phthalate in rats was submitted. Pregnant females were treated by intraperitoneal administration of 0, 320, 640, or 1180 mg/kg/day on days 5, 10, and 15 of gestation. The incidence of fetal skeletal abnormalities was increased in all treatment groups. The high-dose group exhibited an increased number of resorptions and a decreased number of live fetuses [**since no information about maternal toxicity was provided, it is difficult to interpret these results].**
- **Dimethicones** are linear chains of dimethylpolysiloxane (DMPS) which have terminal trimethylsilyl groups. Dimethicone 1000, a component of the enteric coating in the drug product, has a viscosity 1000 cs (centistokes). The dimethicones used in the toxicity studies varied in size and viscosity. Dimethicone 1000 was tested in only one of these studies. **Silicone compounds** are not readily absorbed from the gastrointestinal tract. Following injection of [^{14}C]dimethicone fluid in the hind limb of rats, the radioactivity was distributed primarily in the gastrointestinal tract, and no evidence of metabolism was observed. When [^{14}C]dimethicone was administered through i.p. injection in rats, the following distribution of

radioactivity was observed at 25 days after dosing: 51% in adipose tissue, 27% in gastrointestinal tissues, and 15% in liver. The minimum lethal oral dose of dimethicone 200 (50 cs), dimethicone 550 (75 cs), dimethicone 702 (35 cs), and dimethicone 200 (350 cs) in rats is greater than 30 mg/kg. A 76-week dietary toxicity study of a silicone antifoam compound (94% polydimethylsiloxane silicone oil and 6% silicone dioxide) was performed in mice. Three groups were given diet containing 0, 0.25%, or 2.5% of the test article. The dose levels in the treatment groups were estimated to be 580 and 5800 mg/kg/day. Mortality was increased in the 5800 mg/kg/day females. **No target organs of toxicity were observed. The no effect dose was 580 mg/kg/day** [again, this study is of limited usefulness for assessing the toxicity of dimethicones, due to the small number of organs/tissues examined].

- Dr. Joseph notes that brief summaries of oral toxicity studies of dimethicone in rats were submitted. Female rats were treated with 1, 2, 5, 10, 12, and 20 g/kg/day dimethicone 200 fluid (350 cs), administered by gavage. The animals were dosed 20 times during a 28-day period. **No treatment-related effects were observed at any dose.** A 90-day dietary study in rats was performed using dimethicones with viscosity values of 50, 350, 1000, 10,000, and 60,000 cs. The rats were given a diet containing 1% dimethicone**. No treatment-related effects were observed.** A 2-year dietary study in rats was performed using dimethicone antifoam A. The rats were given a diet containing 0.3% of the test article, yielding an estimated dose of 150 mg/kg/day. **No treatment-related effects occurred** [once again, since no detail of the methods used in these oral toxicity studies of dimethicone in rats was provided, is it difficult to assess the quality of these evaluations].
- A 6-month dietary study of dimethicone antifoam A in dogs was performed using dose levels of 0, 300, 1000, and 3000 mg/kg/day. **The livers from all dimethicone-treated dogs had deposits of bile. The amount of bile present in Kupffer cells and hepatocytes was dose related.** In the 3000 mg/kg/day group, bile was also deposited in the interlobular bile ducts. The significance of the bile deposits is unknown. A no effect dose was not established in this study, due to the bile deposits in liver. However, dimethicone antifoam A was well tolerated at all dose levels [NOTE: histopathology was performed in this study, but it was not stated which organs were examined. It is therefore difficult to assess the quality of this study].
- Brief summaries of reproductive toxicology studies of **dimethicone 360** were submitted. In a Segment I study, rats were treated subcutaneously with 0, 20, or 200 mg/kg/dose, administered three times per week. One half of the pregnant females were sacrificed on day 13 of gestation and the remaining pregnant females were allowed to give birth and nurse their pups for 21 days. **Dimethicone 360 had no effects on the dams, fetuses, or pups.** Segment II studies were performed in rats and rabbits using dose levels of 0, 20, 200, and 1000 mg/kg/day (route of administration not stated). Pregnant rats were treated on days 6 to 16 of gestation, and pregnant rabbits were treated on days 6 to 18 of gestation. **Dimethicone 360 was not teratogenic in either species.** No signs of maternal toxicity were observed. In a Segment III study, rats were treated from day 15 of gestation through day 21 of lactation with 0, 20, 200, or 1000 mg/kg/day (route of administration was not stated). A decrease in the number of live pups was observed at 200 and 1000 mg/kg/day.
- Limited information on the PKs of **PEG-4000** (polyethyleneglycol-4000) was provided. It is worth noting that the absorption of orally administered PEG-4000 is known to be extremely low. At seven days after oral administration of [^{14}C]PEG-4000 in rats, 4.1% of the total radioactivity was recovered in urine and 81.9% was recovered in feces. Following

intravenous administration of [^{14}C]PEG-4000 in rats, the excretion of total radioactivity was 61% and 20% in urine and feces, respectively, at seven days post-dose. Brief summaries of repeat-dose toxicity studies of PEG-4000 were submitted. In a 3-month dietary toxicity study in rats, the no effect dose was 4% (approximately 2400 mg/kg/day). Reduced body weight was observed in rats given 8% PEG-4000 (ca. 4800 mg/kg/day). The no-effect dose in 4-month dietary toxicity study in rats was 5% (ca. 3000 mg/kg/day). Reduced bodyweight and increased liver weight occurred in rats given 10% PEG-4000 (ca. 6000 mg/kg/day) in this study. In a 2-year dietary toxicity study in rats, the no-effect dose was 4% (ca. 2400 mg/kg/day). Reduced bodyweight was observed in the group given 8% PEG-4000 (ca. 4800 mg/kg/day). In a 1-year dietary toxicity study in dogs, the no-effect dose was 2% PEG-4000 (ca. 800 mg/kg/day), which was the only dose tested. A 12-month I.V. toxicity study in dogs was performed using dose levels of 0, 10, 30, or 90 mg/kg/day PEG-4000. The no-effect dose was 90 mg/kg/day [the Pharmacology/Toxicology reviewer notes that these studies are of limited usefulness in evaluating the toxicity of PEG-4000, due to the small number of organs/tissues examined in these studies].

- Studies on the distribution, metabolism, and excretion of **mineral oil** in rats were submitted. The distribution of total radioactivity was mostly limited to the gastrointestinal tract contents following oral administration of [^{3}H]-mineral oil in rats (80% at 8 h post-dose). Both [^{3}H]-mineral oil and [^{3}H]-metabolites with increased polarity were detected in tissue extracts. At two days after oral administration of [^{3}H]-mineral oil in rats, about 80% of the total radioactivity was recovered in feces. The cumulative urinary excretion was 7 to 8% during one week post-dose. Following I.P. administration, 11% of the total radioactivity was excreted in feces and 8% was excreted in urine at eight days post-dose [these results suggest that [^{3}H]-mineral oil is poorly absorbed following oral administration in rats].
- The submitted toxicology studies of mineral oil consisted of chronic inhalation studies in mice, rats, gerbils, dogs, and rabbits. Oil accumulation in bronchiolar and alveolar macrophages was the most common effect in these studies [the MTL agrees with Dr. Joseph's conclusion that it is unlikely that these observations are relevant to the potential toxicity associated with oral administration of mineral oil].
- In his review, Dr. Joseph notes that the light mineral oil that is used as an excipient in the Sponsor's drug product is described as **"medical white mineral oil",** or "paraffinum perliquidum". White mineral oil may be safely used in foods provided that it is a mixture of liquid hydrocarbons (essentially parafinic and naphthenic in nature), meets the test requirements of the USP (United States Pharmacopeia) XX (1980, pg. 532) for readily carbonizable substances, meets the test requirements of USP XVII (pg. 400) for sulfur compounds, and meets the specifications prescribed in the "Journal of the Association of Official Analytical Chemists" (Vol. 45, pg. 66, 1962) for added antioxidants (21 CFR 172.878).
- Given that an adequate dose regimen for the Sponsor's drug product may require the daily ingestion of a large number of capsules, the potential toxicity due to the excipients as well as the drug substance should be considered in the overall safety assessment of this product. In Dr. Joseph's opinion, the incidence of **fibrosing colonopathy associated with high dose levels of PEPs** in CF patients supports this viewpoint. It is noteworthy that an excipient present in certain delayed-release PEPs is suspected of being involved in the pathogenesis of

fibrosing colonopathy, based on evidence from animal studies. This excipient, **Eudragit®** L30D55 (**methacrylic acid copolymer), is not present in Creon® Minimicrospheres®.**

- The maximum daily dose of the major excipients in Creon® Minimicrospheres® can be estimated based on a maximum recommended daily dose of 20,000 lipase units/kg, which would result in the ingestion of 60 Creon® 20 capsules/day in a 60-kg adult and 20 capsules/day in a 20-kg child. The maximum dose levels of the **major excipients** for both adults and children are estimated to be as summarized below.

EXCIPIENT	Maximum dose level for both Adults and children [mg/kg/day]
PEG-4000	75
Light mineral oil	14.1
Hydroxypropylmethylcellulose phthalate	97.2
Dimethicone 1000	2.5
Dibutyl phthalate	8.2

- It is to be noted that the submitted toxicity studies of PEG-4000, light mineral oil, hydroxypropylmethylcellulose phthalate, dimethicone 1000, and dibutyl phthalate were **deficient in the methods used** (**e.g. incomplete histopathology).** However, there is no indication from these studies that these excipients are likely to produce toxicity in patients treated with Creon® Minimicrospheres®, **even at the highest recommended dose levels.** The observed no effect doses in the chronic toxicity studies of the excipients exceeded the potential maximum human dose by greater than 10-fold. PEG-4000 and light mineral oil (white mineral oil) are approved as direct food additives (21 CFR 172.820 and 21 CFR 172.878, respectively). Dimethicone 1000 is a form of dimethylpolysiloxane, which is approved as a secondary direct food additive for use as a defoaming agent (21 CFR 173.340). Furthermore, **there is extensive human experience with Creon® Minimicrospheres®,** which was initially marketed in Germany starting in 1990. This product has been marketed in the United States since 1993 as an OTC product. The Sponsor claims that fibrosing colonopathy is not associated with the use of Creon® Minimicrospheres® [see Dr. F. Gibril's Clinical Review of NDA 20-725 and the Overall Safety Section in the current review].
- The drug product also contains other excipients. These include gelatin, FD&C Blue No. 2, titanium dioxide, iron oxide, shellac, soya lecithin, and 2-ethoxyethanol. Brief comments on each of these excipients are included next.
- **Gelatin** is defined as a food (21 CFR 170.3(n)(22)). Thus, **the ingestion of gelatin capsules, even in the large numbers needed for Creon® Minimicrospheres®, is considered to be safe.**
- **FD&C Blue No. 2** is an approved color additive for drugs (21 CFR 74.1102), and is present only in Creon® 5 capsules. This color additive is considered to be safe when used in amounts consistent with current good manufacturing practice. The ADI (acceptable daily intake) is 0 to 17.0 mg/kg, as recommended by the Joint Expert Committee on Food Additives of the

WHO. The maximum potential dose of FD&C Blue No. 2 associated with use of the drug product is estimated by the Sponsor to be (b) (4) mg/kg/day, based on the ingestion of 60 Creon® 5 capsules in a 60-kg adult or 20 Creon® 5 capsules in a 20-kg child. Thus, for FD&C Blue 2, **the estimated maximum dose level is well within the limits of the ADI.**

- **Titanium dioxide** is an approved color additive for drugs (21 CFR 73.1575). The quantities present in the drug product are consistent with current good manufacturing practice. The estimated maximum dose level is estimated to be (b) (4) mg/kg/day [based on the ingestion of 60 Creon® 5 capsules/day in a 60-kg adult and 20 capsules/day in a 20-kg child].
- **Iron oxide** is approved as a color additive for drugs in an amount not to exceed 5 mg/day of elemental iron (21 CFR 73.1200). The maximum daily intake of iron oxide (and elemental iron) associated with the clinical use of Creon® Minimicrospheres® can be estimated by assuming a maximum daily ingestion of 60 capsules for a given dosage form. The maximum daily dose of iron oxide in Creon® 5, Creon® 10, and Creon® 20 will be (b) (4) mg, respectively. These dose levels are approximately equal to the following daily doses of elemental iron: (b) (4) mg for Creon® 5, Creon® 10, and Creon® 20, respectively. **Thus, the maximum daily intake of iron oxide associated with the administration of Creon® Minimicrospheres® will exceed the approved maximum daily intake (5 mg elemental iron/day).** This information is of interest because chronic exposure to excess iron causes **increased iron absorption from the gastrointestinal tract and elevated levels of transferrin.** Chronic iron overload can lead to an increased synthesis of ferritin in hepatocytes. When the rate of ferritin synthesis in liver exceeds the **rate at which lysosomes can process iron for excretion, the lysosomes can convert ferritin into** hemosiderin, which remains within cells as a stored form of iron. Iron accumulation in liver, pancreas, endocrine organs, and heart are characteristic of chronic iron overload. Thus, disturbances in liver function, development of diabetes mellitus, and abnormalities in endocrine and cardiovascular function are symptomatic of **iron overload**. At the cellular level, iron overload produces lipid peroxidation and consequent damage to mitochondria, microsomes, and other cellular organelles. The maximum daily intake of elemental iron associated with the use of Creon® Minimicrospheres® is estimated to be (b) (4) mg, whereas the Recommended Daily Allowance in adult males and females is 10 mg and 15 mg, respectively. Thus, Creon® must be administered with caution in patients with alterations of iron metabolism.
- **Shellac and 2-ethoxyethanol (ethylene glycol monoethyl ether)** are used as ingredients in the imprinting ink for the drug product. Both of these ingredients are approved for use in inks for marking food supplements in tablet form, gum, or confectionery (21 CFR 73.1(b)). **Soya lecithin** is also an ingredient in the imprinting ink. **Lecithin** is approved for use as **a food ingredient** with no limitation other than good manufacturing practice, and is categorized as GRAS (21 CFR 184.1400).

Summary/Conclusion on Animal Pharmacology/Toxicology

The pharmacologic activity of Creon® Minimicrospheres® was documented in the minipig model of exocrine pancreatic insufficiency. Creon® administration improved digestion of fat, protein, and starch. No evidence of enzyme absorption was shown in pancreatic duct-ligated pigs after

oral administration of the product. The drug substance produced no effect on gastrointestinal motility in mice.

Oral toxicity studies of the drug substance were performed in dogs, using treatment periods of one and nine months. Changes in small intestine and thyroid were observed in the 1-month study. Administration of 4000 mg/kg/day in the 9-month study increased incidence and severity of fat accumulation in liver. Lesions in the large intestine and thyroid were also observed in the treatment groups. Also submitted were toxicology studies of the excipients. From the detailed and comprehensive review of the evidence by Dr. Joseph, the results of the toxicity studies of the drug substance and excipients do not present a significant safety concern.

There are no pre-clinical safety issues relevant to clinical use.

III. Human Pharmacokinetics and Pharmacodynamics

The pancreatic enzymes in Creon® are enteric-coated to resist gastric inactivation. Pancreatic enzymes are intended for action in the lumen of the GI tract. Therefore formal bioavailability/bioequivalence studies are not useful.
Alternative means of evaluating drug availability at the site of action have been utilized. These approaches include the assessment of **ex vivo activity of pancreatic enzymes** in gastric and duodenal aspirates and assessing $^{13}CO_2$ and H_2 excretion using the breath test as a marker of pancreatic enzyme activity. The following is excerpted from the Clinical Pharmacology and Biopharmaceutics review by Dr. Suliman I. Al-Fayoumi, dated September 24, 2003. The following two events, occurring during the development plan are worth mentioning:

- **1994**: During a 6/14/94 pre-NDA meeting, the Agency requests the sponsor determine the bioavailability of the enzymes at the site of action for NDA submission.
- **1996**: The Agency states that the $^{13}CO_2$ breath test bioavailability study may be acceptable for submission in support of in vivo bioavailability of the Creon® Minimicrospheres product (letter dated 2/27/96). The Agency did recommend nevertheless that the sponsor needs to establish their own correlation between lipase output in the duodenum and post-prandial the $^{13}CO_2$ breath test.

1. Nature of the formulations

There are three strengths of the Creon® drug product currently proposed in this NDA, Creon® 5, 10 & 20, representing 5000, 10000 & 20000 units of **labeled lipase activity**, respectively. The coated **minimicrospheres (pellets)** used in the manufacture of these strengths of Creon® are identical. The individual strengths are formulated by varying the quantity of enteric-coated pellets encapsulated in different sizes of hard gelatin capsules. The qualitative composition of the Creon®10 capsule is given in Table 6.

Table 6

NDA 20-725

Qualitative composition of the Creon®10 Capsule*

INGREDIENT	AMOUNT (mg/capsule)
Pancreatin	(b) (4)
PEG-4000	
LMO	
HPMCP 55	
Dibutylphthalate	
Dimethicone 1,000	
Fill weight	

* Composition of the formulation used in study Kreo-629 ($^{13}CO_2$ breath test), which is **compositionally identical** to those used in the clinical trials and the proposed to-be-marketed formulation.

2. Summary review of Biopharm Submission

In the current NDA, the sponsor submitted results of study Kreo-629 designed a) to evaluate the efficacy of pancreatic enzyme replacement therapy in children with CF and b) to validate the $^{13}CO_2$ -hiolein[17] test as a diagnostic technique for the quantitative assessment of exocrine pancreatic insufficiency. In addition, the application included the sponsor's proposed dissolution test method and specification.

a. Study Kreo-629[18]

- 11 male and female children with documented CF (4 M, 7 F, age 10.2 ± 3.0y) received single daily doses of 1,500 lipase units/kg of Creon Minimicrospheres (batch no. 042M) for 6 days followed by placebo for 6 days.
- 12 healthy children (6 M and 6 f, age 11.5 $\pm$ 2.4y) served as control. These healthy children received no pancreatic enzyme treatment and only participated in the first treatment period.
- As mentioned in Table 6, the Kreon capsule formulation used in this study is **identical** to that used in the clinical trials submitted under NDA 20-725.
- The study was conducted in a double-blind, non-randomized, single center, two-period, fashion.
- In each treatment period, the $^{13}CO_2$ breath test was performed following administration of a standard test meal of 1.5 g/kg rice cookies (given with 1 mg/kg ^{13}C-labelled hiolein)

[16]Hiolein is a mixed triglyceride that is a specific substrate for the lipase enzyme.

[18] ***"$^{13}CO_2$ BREATH TEST WITH ^{13}C-LABELLED HIOLEIN FOR THE NON-INVASIVE DETRMINATION OF EXOCRINE PANCREATIC FUNCTION IN HEALTHY SUBJECTS AND IN PATIENTS WITH CYSTIC FIBROSIS: EFFICACY ASSESSMENT OF PANCREATIC ENZYME REPLACEMENT IN CHILDREN WITH CYSTIC FIBROSIS"***.

on day 5. In addition, stool was collected on days 4, 5 and 6 and analyzed for fecal weight and fat and chymotrypsin content.

- All collected breath samples were assayed using the **$^{13}CO_2$-hiolein breath test** and the **rice breath hydrogen (H_2) test.** The $^{13}CO_2$-hiolein breath test allows estimation of **luminal lipase activity** in the form of $^{13}CO_2$ concentration in expired air following oral administration of the ^{13}C-labelled substrate hiolein. The rice breath hydrogen (H_2) test is a useful measure of **amylase activity** since rice flour is believed to be completely degraded in the intestine of healthy subjects to end products including H_2 gas, which is subsequently excreted via the lungs.
- Overall, as shown in Table 2 of Dr. Al-Fayoumi's review, administration of Creon® in CF patients results in a statistically significant increase in $^{13}CO_2$ breath excretion relative to placebo treatment between h 3 & 24 post-dose. No statistically significant difference was demonstrated on H_2 test (indicator of chymotrypsin activity) at any time point. Nevertheless, a number of deficiencies preclude any definitive conclusions from this study as to the efficacy of Creon® in exocrine pancreatic insufficiency. Biopharm deficiencies are listed in Appendix 2 of Dr. Al-Fayoumi's review.
- The sponsor cited two main references in support of the utility of the breath test methodology as an accurate indicator of **duodenal lipase activity.** The first (Vantrappen et al., 1989) reported an excellent correlation (r=0.89) between post-prandial $^{13}CO_2$ breath excretion and duodenal lipase output in both normal subjects (n=25) and patients with pancreatic disease (n=29) after oral administration of a ^{13}C-labeled mixed triglyceride. The second (Kato et al., 1992) reported a significant correlation ($p < 0.01$) between measurement of $^{13}CO_2$ in breath and duodenal output of lipase, as determined via a traditional intubation method. In response to an Agency request for documentation in support of assay validation of the $^{13}CO_2$ breath test (letter dated 10/15/97), the sponsor referenced an additional publication (Caspary et al., 1996) where a hyperbolic relationship was demonstrated between duodenal lipase activity and peak delta over baseline, which was similar to that reported by Vantrappen et al. The sponsor contended that ample evidence existed in support of the utility and value of the $^{13}CO_2$-hiolein breath test as an indicator of duodenal lipase activity. However, in his Biopharm review, Dr. Al-Fayoumi noted that given the high variability and scatter observed in the breath test data, a more relevant comparison appeared to be the one between Creon® vs. placebo treatment as opposed to treated CF patients vs. healthy subjects. Data on differences between Kreon and placebo treatments on AUC of delta and H_2 values in CF patients (Table 4 in Dr. Al-Fayoumi's review) suggest that administration of Kreon in CF patients resulted in statistically significant increase in $^{13}CO_2$ breath excretion relative to placebo treatment between h 3 & 24 post-dose. No statistically significant difference was demonstrated on H_2 test (indicator of chymotrypsin activity) at any time point.

- Dr. Al-Fayoumi concludes that given the substantial shortcomings of the $^{13}CO_2$ breath test, the findings in Study Kreo-629 do not conclusively support the efficacy of Creon® in the treatment of exocrine pancreatic insufficiency[19]. Study shortcomings are:

[19] Clinical data stands on its own as the ultimate judge with respect to the efficacy of Creon in the treatment of exocrine pancreatic insufficiency.

1. *The proposed specifications for release in the buffer stage at the end of shelf life should be the same as that as the initial stage High variability in data*
2. *An alternate mode of administration of Creon® Delayed Release Capsules such as sprinkling the pellets on soft foods should be supported by appropriate in vitro/in vivo data.*
3. *Study Kreon-629 has significant deficiencies and does not support the proposed language in the labeling. Those deficiencies have to be adequately addressed before results from the study as stated In the label. The deficiencies include:*
    - *High variability in the $13CO_2$ excretion data..*
    - *No documentation of the dose actually taken by subjects.*
    - *The Small number of subjects (11 CF patients and 12 healthy subjects) with stool collection done in only 7 of 11 CF patients.*
    - *Lack of adequate validity of the $^{13}CO_2$ test.*
    - *A wide range of doses administered in pediatric subjects and CF patients only, which may have contributed to the high variability observed in the study results.*
    - *Discrepancies between findings of the stool fat analysis in the study and the $^{13}CO_2$ breath test findings.*
4. *Publications suggest that $^{13}CO_2$ breath test may be a useful measure of duodenal lipase activity. However, assay validation is still needed to insure adequate controls to allow for valid conclusions.*
5. *Administered dose was 1,500 lipase U/kg with patients ranging in weight from 20 to 50 kg,*
6. *Study conducted in pediatric subjects and CF patients only, which may have contributed to the high variability observed in the data.*
7. *Findings of the stool fat analysis in the study, considered to be a clinically relevant marker of the efficacy of Pancrelipase preparations in treating exocrine pancreatic insufficiency, do not appear to corroborate the mean $^{13}CO_2$ breath test findings as no significant differences were observed between Creon and placebo treatments. In fact, if Creon® and placebo treatments were compared on medians, which might be more appropriate given the considerable variability, there are hardly any differences between the two treatments.*

b. Dissolution Test Methodology

While addressing this issue, the Biopharm reviewer attempts to answer the following question: "Is sponsor's proposed *in vitro* dissolution test method acceptable as a surrogate of *in vivo* drug release for QA/QC purposes"? It is important to note that the sponsor developed their proposed dissolution test methodology, which involves the three stages that follow, prior to publication of the USP monograph for Pancrelipase Delayed-Release Capsules in May 1995.

1) **Acid Stage:** 12 units of Creon Delayed-Release Capsules are placed in 800 ml of simulated gastric fluid (without enzymes) in apparatus I (basket) at 100 rpm for 120 min and the solution is sampled at the end of the incubation. The proposed specification for this stage is NLT (b) (4) of labeled amount of lipase activity remaining in test sample.

2) **Buffer Stage I:** At the conclusion of the acidic test stage, 2 g of the minimicrosphere beads are transferred to 600 ml of NaH_2PO_4 buffer (pH 5.0) in apparatus I (basket) at 100 rpm for 60 min. There are no proposed specifications for this stage.

3) **Buffer Stage II:** At the conclusion of buffer stage I, pH of the solution is adjusted to 6.0 and the solution is sampled at 30 & 60 min. The proposed specification for this stage is NLT (b) (4) of the labeled amount of lipase activity within 30 min at pH 6.0.

Dr. Al-Fayoumi notes that the sponsor's rationale in selecting the proposed dissolution test method was that the USP method is not sufficiently discriminating as it is designed to provide information on both resistance to gastric fluid and enzyme release in a single step. Thus, a low pancrelipase activity may possibly be due to either decreased release of the enzymes or deterioration of the enteric coating. The sponsor's proposed dissolution test method, on the other hand, allows differentiation between resistance to gastric fluid and enzyme release. The sponsor conducted a study to compare the USP method with their proposed dissolution test method using 3 batches of Creon® Delayed Release Capsules. A series of graphs in Dr. Al-Fayoumi's review s demonstrate side-by-side comparison of the resultant lipase release curves with both USP and the proposed dissolution test methods.
Details of Dr. Al-Fayoumi's comments follow. The lipase dissolution data demonstrate that the USP method consistently results in 10 to 15 % lower dissolution relative to the sponsor's proposed dissolution method [(b) (4) actual activity, respectively]. The data additionally demonstrate that the Creon batches tested conformed to specifications of the USP dissolution methods as well as the proposed dissolution test method. It was also determined that the enzyme release depends on the sample amount in the range of (b) (4) g. Sample amounts beyond (b) (4) g seemed to give results that were independent of the sample amount. Other parameters such as type of apparatus, pH of the pre-treatment medium, sampling time and buffer composition did not appear to have any significant impact on the dissolution of the minimicrospheres (pellets).
Dr. Al-Fayoumi concluded that the sponsor's proposed dissolution test method is comparable to the USP method and is deemed acceptable. The sponsor's proposed dissolution test method and specifications appear to be acceptable as a surrogate of *in vivo* release for QA/QC purposes.

The Biopharm reviewer's recommendation is that from the viewpoint of OCPB, the submission is acceptable provided that a satisfactory agreement is reached on the package insert between the Agency and the sponsor.
NOTE: The Agency's proposed revisions to the Clinical Pharmacology-related sections of the Creon® package insert will be addressed after the sponsor has addressed deficiencies from all disciplines.

3. Conclusions/Recommendations

Dr. Al-Fayoumi notes that the application contains a proposed recommended starting dose in CF patients of 1,000 USP Lipase U/kg/meal for children < 4y of age and 500 U/kg/meal for those > 4y of age. Specific proposed dosage recommendations for other exocrine pancreatic insufficient disorders have not been proposed. Three compositional dose strengths of Creon® are proposed: 5, 10, and 20, which correspond to dose strengths of 5000, 10000 and 20000 USP Lipase U, respectively. In the $^{13}CO_2$ breath test study, a statistically significant difference on $^{13}CO_2$ excretion was demonstrated between Creon® and placebo treatments. However, in the Biopharm reviewer' s opinion several deficiencies exist which preclude definite conclusions. These deficiencies listed at the end of III.2.a. above, which should be forwarded to the sponsor, include: high variability, lack of assay validation, small sample size [n = 11] and the absence of any documentation of the dose actually taken by patients. An additional conclusion based on Dr. Al-Fayoumi's review is that the proposed dissolution test method is acceptable. However, the proposed specification for release in the buffer stage at the end of the shelf life should be the same as that at the initial stage. The specific wording of the Biopharm comments that should be communicated to the sponsor is found on page 4 of Dr. Al-Fayoumi's review.

IV. Description of Clinical Data and Sources

In her clinical review of NDA 20-725, dated September 30, 2003, Dr. Gibril provided detailed information on:

A. Overall Data, B. Tables Listing the Clinical Trials, C. Postmarketing Experience and D. Literature Review.

Brief highlights from this information are included below. In this section of the current review, highlights from the Statistical Review by Dr. Wen-Jen Chen, dated September 23, 2003 are also included.

- The data submitted in support the claim of safety and efficacy of Creon® Minimicrospheres® capsules were obtained primarily from three pivotal trials conducted by Solvay Pharmaceutical, Inc. for two indications:

    1. Two trails [**S2233101 and S2233102**] in support of the indication for treatment of steatorrhea in Cystic Fibrosis (CF) patients (pediatric and adult) with EPI.
    2. One trial [**223.2.01**] in support of the indication for treatment of steatorrhea in Chronic Pancreatitis (CP) patients with Exocrine Pancreatic Insufficiency (EPI).

- A list of the 3 pivotal trials is given in Dr. Gibril's Table 1. The information provided includes trial design, treatment duration, age and gender. It is noted that in these trials, a total of 101 patients were randomized to double-blind treatment. The mean age was 12y for pediatric/adolescent CF, 23y for adult CF and 51y for CP. A list of supportive studies one for CF (K245.5002) and one for CP (K2455005) is given in Dr. Gibril's Table 2. But other than perhaps for safety, the data from these not well-designed studies are of little value when assessing efficacy and were not reviewed in detail by the Medical Officer.

A. POST-MARKETING EXPERIENCE

- According to the information provided by the sponsor, Creon® capsules are registered for marketing in over 50 countries worldwide and are available in both the MS and MMS formulations; none of these products have been withdrawn from the market due to safety concerns. Post-marketing adverse AE reports were selected from the sponsor's database, from spontaneous reporting, from literature and from authorities. The events were grouped by body system using COSTART terminology. Overall, the sponsor's conclusions based on the original submission (P-M experience from October 21, 1982 to March 15, 1997), remained unchanged when examining data from the up-date (additional P-M experience covering the period of March 16, 1997 to September 30, 2001). From worldwide sales volume (03/16/97 to 09/39/01) of pancreatin, it has been estimated that each patient received a mean dose of 2.2-g pancreatin/day and has continued treatment for an average of 365 days.
- The number of AEs by time-period their most frequent occurrence is summarized below.

Creon®: Post-marketing Adverse Event[a] Summary

Total number of Events for Period 1982 to 1997	376[b]
Total number of Events for Period 1997 to 2001	289
Most commonly reported AEs (equal or more than 5 reports)	
• **Gastrointestinal Tract[c]**	
- Abdominal pain	32
- Diarrhea	27
- Flatulence	14
- Constipation	8
- Malabsorption syndrome	8
- Nausea	7
- Vomiting	6
• **Skin and appendages[d]**	
- Pruritus	9
- Urticaria	7
- Rash	6
• **Insufficient therapeutic effect[e]**	4

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a) Includes Serious and Non-Serious Adverse Events
b) Experienced by 231 foreign and domestic patients
c) These are comparable in frequency and quality with the figures given in the original submission.
d,e) These have decreased slightly as compared to the original report. The sponsor proposes that these are typically seen for any drug involving spontaneous reports and may be related to the natural probability and occurrence of pork sensitivity in the general population

B. SERIOUS ADVERSE EVENTS (SAEs) SUMMARY

- As mentioned in Dr. Gibril's clinical review, intestinal stenosis, intestinal obstruction, stenosis of colon and colitis were event categories, which yielded the greatest number of SAE reports. The stenosis cases are addressed under the fibrosing colonopathy heading (see below). The 5 reported cases of colitis listed other pancreatic enzyme products as the suspect medications. Other colitis cases involved concomitant antibiotic use for pulmonary infection. The sponsor indicated that the likelihood of pancreatic enzyme involvement in these cases is inconclusive due to lack of available data.
- 4 deaths, including 1 from the 1997 Clinical Document, were reported. These are briefly summarized below.

1. PANC003970007

This was a 14-y-old F with severe pulmonary disease. She died 9 months into a study investigating the relative contribution of optimal nutritional support in CF. Children in this independent study were given enteric-coated Creon® MS in an individualized dosage, and were instructed to take in a high-fat diet. A telephone call to the author of the report revealed that the death was not related to the drug product, but rather to the child's underlying pulmonary condition.

2. PANC01888980002

This was 86-y-old M with a history of mitral regurgitation and cardiomyopathy. He was hospitalized for aggravated cardiac insufficiency while he was treated with a total of five suspected drugs (pancreatin, fluvoxamine, tinaptine, acetylsalicilate lysine, and digoxine). All drugs were regarded as having a remote or unlikely causal relationship to the occurrence of the AE. The patient died 19 days after the onset of the reaction. No further information is available.

3. **PANC00399001346**

This case occurred in a 70-y-old patient (unknown sex) with a history of neuropathy. After 2.5 y treatment with Creon® for CP and an overall good condition the patient was hospitalized for treatment of anemia, received blood transfusion and after 2 days in the hospital fell. He suffered subarachnoidal hemorrhage and died 12 days later. The reporter assessed this death as unrelated to Creon®.

4. PANC00301001069

A 70-y-old F with history of adenocarcinoma experienced anemia and thrombocytopenia while she was being treated with five suspect drugs (Creon®, omeprazole, prednisone, bromazepam, and gemcitabine). The AEs occurred on an unspecified date. The platelet had decreased to 12000/ul but then started to improve. All drugs were stopped but the patient died on an unknown date. Her death was not linked to the reported AEs. All drugs were regarded as having an unlikely causal relationship to the occurrence of the AEs, including death.

- As mentioned in Dr. Gibril's clinical review, the sponsor concluded that overall, there were few SAE reports in the post-market experience relative to the volume of drug used worldwide. Creon® therapy can be regarded as safe in treatment of EPI associated with CF and CP.

C. FIBROSING COLONOPATHY (FC)

There are safety problems associated with the use of pancreatic extracts. Common and usually non-serious side effects are gastrointestinal in nature and include diarrhea, nausea, stomach cramps and pain. Other manifestations include hyperuricosuria, hyperuricemia, obstipation and intestinal obstruction[20]. FC is characterized by marked submucous fibrosis and symptomatic strictures of the proximal colon. The term "FC" was introduced to describe this complication of cystic fibrosis involving stricture or pre-stricture stare with varying degrees of stenosis in the colon. The pathogenesis of this process remains uncertain. Although this rare disease occurs predominantly in young children with cystic fibrosis, cases of intestinal stricture and obstruction

[20] It appears that these side effects are addressed at different extents in the labeling for a number of currently marketed products.

have been observed in at least one adult and one child without cystic fibrosis treated for prolonged periods with high concentrations of enteric coated pancreatic enzymes. It is worth noting that FC does not seem confined to either cystic fibrosis or children. Furthermore, although a history of excessive doses pancreatic enzyme supplementation - usually achieved by consumption of 40,000 lipase units/kg/day or more -is considered the most important risk factor for FC[21], there is at least one instance of a patient that was receiving standard strength preparations but still developed FC[22]. It is also of interest to mention that there are cases of patients with cystic fibrosis and intestinal obstruction following years of abdominal pain; these reports, which long anteceded enteric coated enzymes[23], are associated with surgical findings of cecum embedded in a solid mass of fibrous tissue (very similar to the FC). Also, the issue of which of the components of the enzyme extract produces FC is not settled. An investigator from the Netherlands blamed Eudragit® but evidence in support of this hypothesis is not convincing. Many believe that lipase is the culprit. Lipase, the gold standard of measurement of severity of PEI and the efficacy of treatment, is the main indicator of a product strength. It is however important to reiterate that the enzymes lipase/protease/amylase are in a fixed ratio; when the dose of lipase is increased, the dose of the other two enzymes are also increased; one could speculate that the cause of FC could be in the protease concentration in the tablet/capsule but this theory needs further experimentation. In addition to the high dose pancreas enzyme supplementation, other important risks factors for FC are the inhalation of recombinant human DNAse, the intake of laxatives, H_2-receptor antagonists, corticosteroids, a history of gastrointestinal complaints, all of which correlate with an increased incidence of this disease[24]. Other proposed risk factors are diet per se[25] and the amount of intrinsically produced pancreatic enzymes. Endogenous pancreatic enzymes may have a role in enhancing, even if not initiating, lesions which lead to fibrosis, as shown by animal experiments in which ligation of the pancreatic duct mitigated or delayed the response to ischemia[26].

In the material that follows, the issue of fibrosis colonopathy, as addressed in Dr. Gibril's clinical review, is briefly summarized.

- Using the COSTART dictionary for the occurrence of events that might be related to **fibrosing colonopathy**, the sponsor identified **37** cases/reports in the post-marketing report submitted in 1997, **in all of which pancreatic enzyme therapy was used**; 7 cases were excluded from further evaluation, since in 4, Creon® use was excluded and in 3 Creon® use was not confirmed. In 17 of the remaining 30 cases, a highly probable cause of symptoms other than fibrosing colonopathy was identified [11/17 = DIOS (distal intestinal obstruction syndrome); 6 (PANC002940013, PANC00394007, PANC003940016, PANC003940018, PANC00395001, and PANC003950012) had a probable diagnosis other than FC or DIOS].
- In 13 of the 30 cases, the sponsor reported that there was histological evidence suggestive of fibrosing colonopathy. These cases are summarized in Dr. Gibril's Table 8.6.2.3.5.4.2 of her review. As seen in this Table, during the 12 months prior to surgery for fibrosing colonopathy all of these cases had received other pancreatic supplement products, which

[21] Hausler M et al. First adult patient with fibrosing colonopathy. Am J Gastroenterol 93: 1171-1172 (1998).

[22] Jones F et al. Colonic strictures in children with cystic fibrosis on low-strength pancreatic enzymes. Lancet 346:499 (1995).

[23] Hodson ME et al. Meconium ileus equivalent in adults with cystic fibrosis of pancreas; a report of six cases. BMJ ii:790-791 (1976)

[24] Cited in the 1998 article by Hausler et al (locus cited)

[25] Gavin J et al. Dietary fibre and the occurrence of gut symptoms in cystic fibrosis. Arch Dis Child 76: 35-37 (1997).

[26] Haglund V. Gut ischaemia. Gut 35 (suppl 1): 573-576 (1994).

included: Eurobiol 25000, Nutrizym 22, Pancrease HL, Pancrease MT 25 and Ultrase MT 24, in addition to Creon®.

- According to the sponsor, exposure to Creon® products was limited. In addition, the potentially confounding effect of switching between different brands of enzymes, a notable feature of the UK but not the US case control series needs to be considered. This is exemplified by the following information:
  - 5 cases received Creon® products in the period from 24 to 12 months before surgery for fibrosing colonopathy and then switched to non-Creon® products
  - 5 cases received Creon® 25000 in the period from 12 to 7 months before surgery and then switched to non-Creon products
  - the remaining 3 cases (PANC002940011, PANC002940014, PANC003940004) switched from Ultrase MT 24, Pancrease MT 25 and Pancrease HL, respectively, to Creon® products shortly before surgery
  - 2 of the children who were exposed to Creon® shortly before surgery had already developed symptoms of fibrosing colonopathy on non-Creon products, whereas the third child received Creon® for only 21 days.

From the above-summarized information, the sponsor concluded that there was no case of fibrosing colonopathy confirmed by histology in which Creon® was taken alone.

The clinical review notes that, in addition, the sponsor provided 5 suspected cases of FC, 2 DIOS cases, and 2 cases of colitis that were added to the sponsor's database **since 1997**. The sponsor indicated that in one literature case of FC (Moss et al) and one of (Lloyd-Still et al), the specific product was not referenced. Hence, the use of Creon® product in these 2 literature cases can neither be excluded nor confirmed. Brief clinical summaries of cases not included in Dr. Gibril's Table 8.6.2.3.5.4.2. are given below, to illustrate some points.

PANC00399000418 (Moss et al)

After the use of unknown brand for an unknown period of time an 8-y-old boy with CF presented with chronic diarrhea and cramps. One year later he developed bloody diarrhea. Biopsy with colonoscopy revealed non-specific acute inflammatory infiltrate. One year later he underwent **right colectomy** for a **tight stricture in the cecum, consistent with FC**. He had another surgery for recurrence of FC. One year later persistent narrowing of the remaining colon segment was found.

PANC003990084 (LIoyd-Still, 1996)

A 6-y-old girl, with insulin-dependent diabetes and hypothyroidism presented with severe diarrhea due to EPI 6 months after increasing the dosage of pancreatic enzymes unknown brand until 20000 U lipase/kg/meal. Rectal bleeding occurred and colonoscopy revealed lesions and infiltration with eosinophils. Upper endoscopy revealed **celiac disease.** In spite of this finding, gluten-free diet did not succeed in symptoms relief but only withdrawal of pancreatic enzymes.

The following four suspected cases of FC (PANC002970012, PANC00980002, PANC002980008, and PANC00300001588), 3 with histological confirmation, had received Creon® products in addition to other pancreatic enzyme brands (scanned, amended vol. 1, page 329). Again, the sponsor indicated that there were no cases of FC on Creon® products alone.

The two cases of DIOS were summarized as follows:

S/N

A CF M received treatment with Creon® since birth at a dose < 1000 units/kg/day. At age 13-y he presented with a 7-y history of abdominal pain. On examination he was found to have a mass in the right iliac fossa. US suspicious for intussusception and barium enema revealed a colonic stricture. At surgery a stricture of ascending colon was resected. The histology was consistent with DIOS.

PANC00399002024

A 17-y-old CF F on Creon®5000 lipase units/kg/day presented with a 5-month history of nausea, abdominal pain bloating and intermittent loose stools. A diagnosis of DIOS was made. Symptoms persist despite adjusting the enzyme dose and changing her diet. Creon® was switched to Pancrease.

The sponsor presented another case with intestinal obstruction.

PANC003990001

The patient was a premature infant born with an **intestinal volvulus** which was corrected with surgery. At one month, following diagnosis of CF, treatment was commenced with Creon® 12,000, one capsule daily. Six days latter the infant developed necrotizing enterocolitis with multiple perforations on a bowel loop with volvulus. An ileostomy was created at surgery.

The following three cases of FC were reported in the literature since 1997 and were provided by the sponsor. A summary of these cases is shown below.

PANC002970012 (Fallick et al, 1997)

A 3-y-old cystic fibrosis M was treated with Creon®20 between September 1995 and April 1996 and then switched to Ultrase@MT18. After 4 months of therapy with Ultrase@MT18, the boy began to experience **periumbilical cramping**. Three months later a CT of the abdomen demonstrated a stricture in the proximal ascending colon. A right hemicolectomy was performed and histopathology revealed the **diagnosis of FC** In (b) (6) the child was found by an open bottle of nail polish remover and the mother, believing the child had ingested some of it, administered syrup of ipecac. The patient began to vomit and continued to do so intermittently for 36 h. He then suffered a cardiac arrest and died. The cause of death was given as mesenteric ischemic small bowel volvulus secondary to postoperative adhesions. The physician believed that there was no causal relationship between the use of a pancreatin and the child's death.

PANC002980008

A 9-y-old cystic fibrosis F was treated with Zymase@ from March 1993 until September 1993 and then switched to Ultrase MT (up to 58,000 lipase units/kg/day) for 16 months until November 1994. Zantac was prescribed in September 1994 presumably for abdominal symptoms and Ultrase MT was switched to Creon®20 (27,000 lipase units/kg/day) one month later. Cotazym@ was added to her regime in April 1997. Her family relocated in 1997 and she was seen by a new pediatrician in September 1997 who suspected that her persistent problems with malabsorption, abdominal pain and diarrhoea could be due to **fibrosing colonopathy.** A barium enema in April 1998 showed colonic strictures and a subtotal colectomy was performed. **Fibrosing colonopathy was confirmed on histopathology.**

PANC00300001588 (Bansi et al, 2000)

In her late 40s a non-cystic fibrosis F with gallstone disease suffered an episode of acute pancreatitis following an endoscopic sphincterotomy. Thereafter she was never free of pain and commenced treatment with Creon® in 1988. In 1990, her medication was changed to Pancrease@ (3000 lipase units/kg/day). Because of unrelenting pain she underwent a pancreaticoduodenectomy. To control diarrhea the dose of Pancrease was increased to 5300 lipase units/kg/day. In 1991, treatment was changed to Nutrizym@ GR (17,700 lipase units/kg/day) and then in 1992 to Nutrizym 22 (38,000 lipase units/kg/day). In mid-1995 she developed severe abdominal pain with a possible mass in the right iliac fossa. A diagnosis of Crohn's disease of the ascending colon was made on full-thickness biopsy. She commenced mesalazine 400mg tid and continued treatment with Nutrizym. However, her symptoms persisted and at laparotomy in April 1997, a right hemicolectomy was performed. Histology confirmed **fibrosing colonopathy** of the ascending colon and cecum.

PANC000980002 (O'Keefe, 1996)

A 5-y-old cystic fibrosis Female started treatment with Creon® and then switched to Nutrizym GR in late infancy. At age 2.5 y, she switched to Nutrizym 22 and remained on high doses of this brand (up to 36 capsules per day) for 2 5 y when she presented with frequent soft stools and fecal soiling. An US showed free fluid in the peritoneal cavity and increased colonic wall thickness. The barium enema appearances were suggestive of **fibrosing colonopathy.** Nutrizym 22.was discontinued and the child was switched back to bon ********

NOTE: Dr. Gibril mentioned that the sponsor noted that **fibrosing colonopathy** is not confined to children with CF and, most significantly, the third case illustrates that treatment with

pancreatic enzymes is not a prerequisite for development of the disease. It is also noted that the first two cases were exposed to **Eudragit L30D55-coated pancreatic enzymes.** The second case additionally received mesalamine, a tablet formulation coated with Eudragit L30D55. The third case received only **Eudragit-containing measalazine.** The sponsor further noted that epidemiological and experimental evidence suggests a role for Eudragit in the development of FC as it was induced in the pig exposed to Eudragit alone and in a patient who had never ingested pancreatic enzymes but did receive a Eudragit-coated drug. Therefore, it is reasonable to conclude that Eudragit may, in some way, be associated with the induction of the disease. The sponsor further stated that Creon® brand dose not contain Eudragit, and there have not been any cases of FC in patients treated with Creon® alone at any dose over a period of 19 y, since the introduction of this pancreatic enzyme extract in 1982.

Sponsor's Summary and conclusions on fibrosing colonopathy

[Includes materials on fibrosing colonopathy in sponsor's submission of September 11, 2003][27]. According to the sponsor, no cases of **histologically confirmed fibrosing colonopathy** in which Creon® was taken **alone** were reported. The cases of distal intestinal obstruction syndrome and enterocolitis are not considered to be related to treatment with Creon®.

- From evaluations included in her clinical review, Dr. Gibril concludes that enzyme preparation are generally safe, even though microencapsulated preparations containing large lipase doses of > 20,000 IU per capsule have been withdrawn from the market due to colonic strictures noted in children with CF. Other complications include bloating, abdominal cramps, flatulence, hyperuricosuria, folate and iron deficiency.

- Dr. Gibril carried out a detailed appraisal of the data that are available in the Literature. Included in this Section of her review are concepts related to the epidemiology, etiology, pathophysiology, clinical evaluation and diagnosis, differential diagnosis, as well as accepted principles governing the management of CF and CP in the clinic.
- It is worth reiterating here that the cornerstone of therapy for maldigestion due to EPI is replacement of pancreatic enzymes in the gut to allow for efficient digestion and absorption of nutrients. Porcine or bovine enzyme extracts have been used for decades (> 70 y) to provide pancreatic enzymes. Pancreatic enzyme supplements were first marketed in the form of powder, tablets and capsules and were made up from porcine pancreatic extracts containing lipase, protease and amylase. There are a great number of non-enteric and enteric-coated pancreatic enzyme preparations in the form of powders, capsules and tablets, or in multiunit doses such as pellets, granules and micro-tablets. Pancreatic enzyme supplements formulated as microspheres and micro-tablets coated with an acid resistant film to prevent inactivation of enzymes by gastric acid were introduced in 1970's.
- As noted by Dr. Gibril, there are a number of enzyme products available commercially, both as prescription or OTC products. However, the limitation with enzyme products is

[27] Sponsor's updated response to the information request letter dated 06 June 2003.

that they may vary in potency and pharmaceutical properties. Furthermore, because the enzyme activities vary from product to product, the relative potencies across products are not easily comparable. This constraint makes it difficult to calculate equivalent doses.

V. Clinical Review Methods

In her primary review of NDA 20-725, Dr. Gibril addressed the issue of how her review was conducted, she then proceeded to give an overview of materials consulted in review which was followed by an overview of methods used to evaluate data quality and integrity. One of the important sources of information is the **Dosing in CF according to the CFFCC[28] published in November 1995.** This is reproduced below:

- Weight based enzyme dosing should begin with 1,000 USP lipase units/kg/meal for children < four years of age and with 500 USP lipase units/kg/meal for those over age four
- Dosage should be adjusted according to the severity of the disease, control of steatorrhea and maintenance of good nutritional status.
- Dosage in excess of 2,500 USP lipase units/kg/meal should be used with caution and only if they are documented by three-day fecal fat measurements to significantly improve the coefficient of fat absorption.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with **fibrosing colonopathy**
- Also provided were directions for dosing in other exocrine pancreatic insufficiency disorders.
- Additional important information included in Dr. Gibril's review follows. Selection of an enzyme preparation is to be based on the protease concentration within the preparation, the stability of the enzyme in withstanding gastric acidity, and the timely release of the enzyme in the duodenum from the capsules. As noted above, with all pancreatic enzymes, lipase is destroyed more easily than the protease trypsin. With non-enteric preparation up to 90% of enzyme activity may be lost, and patients may need to take a large quantity of the drug. Concomitant use of proton-pump inhibitors or H_2-receptor antagonists has been recommended to suppress gastric acid secretion. Enteric-coated preparations were designed to prevent acid inactivation within the stomach, and the polymer coating of these preparation dissolves at pH >5.
- Encapsulated enteric-coated microspheres or Minimicrospheres, as in the case of Creon®, are now considered the enzyme treatment of choice. After release from the gelatin capsules, the enteric-coated pancreatin particles distributed within stomach and mix with the chyme to pass the pylorus together with solid food, particles must be approximately 1.4 mm in diameter. An effective enzyme preparation must show rapid release enzymes once a pH of 5.5 has been reached.
- There is a considerable individual variation in enzyme production in patients with EPI and consequently, some patients need large amounts of exogenous enzymes and others small amounts of enzymes to have therapeutic benefit. Although the effectiveness of treatment is usually controlled by clinical symptoms, if treatment responses are unsatisfactory, objective assessment of treatment efficacy is needed with quantitative fecal fat excretion test or coefficient of fat absorption (CFA). This test is useful to assess the effectiveness of lipase replacement.

[28] Cystic Fibrosis Foundation Consensus Conference

- Moreover, in approaching therapy for EPI, it has been reported that the maximal postprandial delivery of pancreatic lipase in a normal state is ca. 140,000 IU per hour for 4h after a meal, and maldigestion supervenes only when < 5% to 10% of the normal maximal enzyme output is delivered to the duodenum. To meet this requirement, approximately 30,000 units of lipase must be delivered to the duodenum during the prandial and 4-h postprandial period with each meal for adequate digestion of fat. In general practice dose is initiated with a minimum amount of enzyme (30,000 IU of lipase) with each meal in and subsequently adjusted according to the individual need. Usually, half the standard dose is given with snack. Although the protein maldigestion appears to be adequately corrected by enzyme replacement therapy, fat maldigestion, whether due to CF or CP, is hardly ever corrected.
- As mentioned above, in CF patients, the dosing is administered according to the US CFFCC recommendations.
- In summary, enzyme preparation are generally safe, even though microencapsulated preparations containing large lipase doses of > 20,000 IU per capsule have been withdrawn from the market due to colonic strictures noted in children with CF. Other complications include bloating, abdominal cramps, flatulence, hyperuricosuria, folate and iron deficiency.
- An inspection of 3 sites participating in the CF trials and enrolling a relatively large number of patients was carried out by DSI. The report was issued on August 26, 2003. Two of the sites participated in Study protocol S2233101, while the other took part in Study S2233102. The overall assessment of findings and general recommendations stated by DSI in this report was that the documentation available showed that the (minor) protocol violations described do not affect the reliability and validity of the data.
- The trials were conducted in accordance with accepted ethical standards.
- The requirement for financial disclosure is waived for the clinical studies because the trials submitted in support of NDA 20-725 were completed prior to the FDA financial disclosure requirements published in February 2, 1999.

VI. Integrated Review of Efficacy

In support of the approval of enteric-coated, delayed release, Creon® Minimicrospheres® capsules, NDA 20-725, the sponsor submitted results from 2 trials in CF and 1 in CP patients with steatorrhea due to EPI. The primary efficacy parameter was the Coefficient of Fat Absorption (CFA). The sponsor concluded that the drug product is efficacious in these three well-designed and well-controlled studies.

This MO reviewer concurs with the sponsor that the submitted two clinical trials demonstrated, in replicable fashion, that Creon20 is effective in the treatment of steatorrhea associated with EPI in patients with CF. Although these data appear generalizable because these were multi-center trials, it is unclear if the study patients are representative of the general pediatric CF population because patients < 7y of age were not included in these trials.

Unlike what is claimed by the sponsor, the results of the trial submitted in support of the use of the drug in CP patients with EPI were not robust, although significant differences using the primary efficacy parameters were demonstrated. Due to the small sample size and the presence

of outliers, small changes with respect to placebo seem to be of less clinical significance. An additional constraint is that there was no significant difference between test medication and placebo in analysis of results of secondary efficacy parameter, i.e. either physician- or patient-rated clinical global impression of disease symptoms (CGID).

- The MO reviewer followed a sound approach to the review of trials in the NDA submission. She carried out a careful examination of the protocol-stipulated methods, with emphasis on study population, dose selection, endpoints, and analytical methods. Results of the three pivotal trials were examined in great and, when appropriate, insightful comments were provided.

- As seen in Table 7, sponsor submitted results of 3 clinical trails for two indications: a) 2 trials for steatorrhea due to EPI, one in pediatric/adolescent (S2233101), the other in adult (S2233102) CF patients and b) one trial in support of steatorrhea due to EPI in CP patients (223.2.01).

Table 7
NDA 20-725
Summary of the three pivotal trials with CREON® MINIMICROSPHERES®

Protocol No.	No. of sites	Study Population	Drug product	Study Design	Total Number of Patients Enrolled	Randomized	Completed
S2233101	6	CF (pediatric/ adolescent)	Creon® 20	Parallel, Double-blind, Placebo-controlled	47	38	37
S2233102	6	CF (adult)	Creon® 20	Parallel, Double-blind, Placebo-controlled	50	36	34
223.2.01	16	Chronic pancreatitis	Creon® 10	Parallel, Double-blind, Placebo-controlled	64	27	27

A. CYSTIC FIBROSIS

1. Study Protocol S2233101

(pediatric and adolescent cystic fibrosis)

- Six U.S. centers participated in this in-patient, outpatient trial set to compare the effectiveness of Creon®20 (20,000 USP lipase units) delayed-release Minicrospheres® to placebo in the treatment of steatorrhea in CF patients (7 to 18y of age) with EPI, who were maintained on a high fat diet.

- The **primary efficacy parameter** was the Coefficient Fat Absorption (CFA), calculated from 72-h stool values and fat intake data from nutritional diaries according to the formula:
  CFA% = Fat intake (g/day) – Fat excretion (g/day) x 100
  Fat intake (g/day)
- The **primary efficacy measure** was change from baseline (open label) to final (double-blind) assessment in the CFA. A total of two 72-h stool collections were scheduled.
- The **secondary efficacy parameters** measured the change from open label Creon20 treatment to double blind treatment for number of bowel movements as well as most frequent stool consistency[29] per stool collection period, and clinical global improvement (CGI)[30].
- As detailed in Dr. Gibril's review, the **study design** was randomized, double-blind, placebo-controlled, parallel group, 2-arm and multi-center, with an open-label run-in phase. Following a one- to two-week screening period, qualified patients entered the open-label phase of the study where they began a controlled high fat diet (at least 100 g /day) while individually adjusting the number of Creon20 capsules per meal (snack) to maximize clinical effect as guided by clinical symptoms. As explained in Dr. Gibril's clinical review, when an optimal dose was reached and maintained for at least 2 days, and after at least 3 days on the high fat diet, patients entered the clinic to begin a 72-h stool collection, during which time the high fat diet was strictly controlled. Based on the value of CFA obtained at the end of the open-label phase, patients were either excluded from further participation in the trial (CFA ≤ 80%), or entered the double-blind phase (CFA was >80%). Qualified patients were randomized to either Creon20 or placebo treatment. The double-blind dose was to be the same as that established during open-label treatment. After a minimum of two days of double blind treatment while on a high-fat diet, patients were admitted to the clinic for the second 72-h stool collection, as shown in Fig. 1 of Dr. Gibril's review.
- The study population consisted of male and female well-characterized CF patients, 7 to 18y of age. The inclusion/exclusion criteria were adequate.

Test medication and dose selection

- **Each Creon20 capsule contained 20,000 USP units lipase, 75,000 USP units protease and 66,400 USP units Amylase.**
- According to the Study Report, the open-label Creon20 dose was individualized for each patient while on a high fat diet using clinical symptoms as a guide. Patients were instructed to adjust the number of capsules taken per meal/snack. The double blind dose was to be the same as that established during open-label treatment. A strict accounting of study medication dispensed to, and received from, was recorded on the CRF.

Statistical Analysis

- As pointed out in Dr. Wen-Jen Chen's statistical review and evaluation, with 40 patients (20 per treatment arm), Type I error rate of 0.05, and standard deviation of 21.54, this trial was to

[29] Stool consistency was rated by the patient as : 1 = hard; 2 = formed/normal; 3 = soft; 4 = watery.

[30] CGI was assessed by the physician at the end of the double-blind treatment phase using a 7-point physician-rated scale : 0= not assessed; 1= very much improved; 2 = much improved; 3= minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse.

have greater than 80% power to detect a difference of 20 points in change from baseline CFA between Creon®20 and placebo. The main patient population analyzed was the ITT, which consisted of all patients randomized into the double-blind phase of the trial who took at least one dose of double-blind test medication.

- The protocol stipulated that a fixed-effect ANOVA 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 $p \leq 0.05$.

Results

- Of the 47 patients screened and entered into the open-label treatment, 38[31] qualified patients were randomized into the double-blind phase [Creon®20, n = 18; placebo, n = 20][32]; 36 of the randomized patients completed the trial [Creon®20, n = 18; placebo, n = 18].
- 16 patients [Creon®20 ,n = 9; placebo, n = 7] had minor protocol deviations, which were not expected to influence results. Dr Chen performed additional efficacy analysis, by excluding 8 patients (4 in each treatment arm) who had irregularities in 72-h stool collections. Removal of these 8 patients from the analysis did not alter the highly significant statistical difference between the comparison groups ($p < 0.001$).
- 38 patients [18 males and 20 females between 7 and 17 y of age, mostly Caucasian (95%), weighing from 22 kg to 60 kg and 112 cm to 170 cm in height] made up the ITT patient population. The latter appeared to be representative of the general pediatric and adolescent population diagnosed with CF with no apparent demographic differences between the two treatment groups. The mean age in Creon®20 group was 12.8y while the mean age in the placebo group was 12 years.
- The test medication dose was individualized for each patient while on a high-fat diet using clinical symptoms as a guide. It is worth reiterating that for each study phase drug dosage was calculated for each patient as the mean number of capsules taken per day multiplied by the **lipase content per capsules** (20,000 units) divided by the weight (kg) at the screening visit. During the open-label phase, the mean daily lipase dose/kg was **7440** [range 1280 to 14983] for Creon®20 patients and **7340** [range 1364 to 15497] for placebo patients. During double-blind treatment phase, the mean daily lipase dose/kg was 7855 [range 1032 to 15782] for patients receiving Creon®20 and **7560** U/kg for patients receiving placebo. As explained in Dr. Gibril's review, **these means were calculated from the number of capsules equivalent to the actual mean lipase dose**.
- The mean duration of exposure was comparable between the two treatment groups during the open-label (18 days) as well as the double-blind treatment phase (7days).
- Using the change in CFA from the open to the double-blind phase of the trial as the primary efficacy parameter, the results of efficacy analysis are summarized in Table 8.

[31] Of these 38 patients, 2 (No. 60207 and No. 60196) discontinued prematurely

[32] Of the 9 patients discontinued from the open-label phase, 7 did not qualify for randomization because they had a CFA < 80%); the remaining 2 withdrew consent.

Table 8
Study S2233101
Changes in Coefficient of Fat Absorption (CFA)
ITT Study Population

	CFA (%)		Therapeutic gain	p-value[b]
	Placebo [n=19]	Creon®20 [n=18]		
Open-label (OL) treatment[a] Mean	87	87		
Double-blind (DB) treatment Mean	52	84		
Change from OL to DB treatment Mean	-35	-3.0	-32	**<0.001**

This Table is based on Table 6 in Dr. Gibril's Clinical Review, with substantial modifications. The mans have been rounded Off, the ± SEM and the ranges have been deleted for simplification of presentation purposes.

a) All patients received Creon®20 capsules during open label treatment, however, sample is broken down by double-blind treatment assignment for comparison.
b) p-value calculated based on ANOVA model with factors for center, treatment, and center-by-treatment interaction.

As shown in Table 8, the mean CFAs of the Creon®20 (87%) and placebo (87%) treatment groups were comparable following the open-label phase in which patients were treated with Creon®20. However, following the double-blind treatment phase, the CFA means for the 2 groups differed: 84% for the Creon®20 group vs 52% for the placebo group. The change in the mean CFA from the open-label phase to the double-blind treatment phase was **clinically** [a therapeutic gain of a CFA of 32%] and **statistically significant** ($p < 0.001$). Furthermore, to address the clinical reviewer concerns regarding deviations in 8 patients additional efficacy analyses, excluding these 8 patients, were performed by Dr. Chen. The result remained even more significant. The change in mean CFA from open-label Creon 20 phase to the double-blind phase almost no change (-2) for patients who continue on Creon®20 and –36 for those randomized (switched) ($p<0.0001$).

- The results of analyses of **secondary efficacy parameters** also showed clinical and statistically significant differences between Creon®20 and placebo in the change for the open-label to the double-blind phase of the trial. Creon®20 was superior to placebo in the 3 evaluated secondary parameters of efficacy: **stool frequency** ($p = 0.002$), **stool consistency** ($p = 0.001$) and **CGI, the clinical global improvement** ($p < 0.001$).

- Regarding **Safety Evaluations**, the most frequent treatment emergent adverse events reported by patients were in the following 3 body systems: body as a whole, respiratory

and digestive. An increase in abdominal pain following double-blind placebo treatment was the largest treatment difference: 2/18 (11%) for Creon®20 and 11/20 (55%) for placebo. There were no differences between the 2 treatment groups in the frequency of other treatment-emergent AEs. The types of AEs reported during this trial were not unexpected for patients with CF. In addition, there were no apparent treatment differences when comparing the change from screening physical examinations and reports of markedly abnormal laboratories or vital signs.

- **NOTE:** The MTL agrees with the conclusion that, under the experimental conditions of well-designed and apparently well-executed Study S2233101, Creon®20 capsules were shown to be safe and effective in controlling the symptoms of fat malabsorption in children and adolescents with cystic fibrosis.

2. Study Protocol S2233102

(Adult cystic fibrosis)

NOTE: The protocol for this trial is identical to study protocol S2233101described in detail above; but the patients in the current study were adult (≥ 18 y). Therefore, the MTL's comments made regarding protocol S2233101 will not be repeated here. It is also important to note that S2233102 was conducted by the same qualified investigators at the same centers as the other CF trial.

RESULTS

- 36 of 50 patients enrolled into the open-label phase at 6 centers were qualified (CFA >80%) for randomization into double-blind phase [Creon®20, n = 18; placebo, n = 18]. Of the 14 patients who were not randomized, 12 were not qualified for randomization according to the protocol stipulated rules (CFA <80%) while 2 experienced AEs (1 = pulmonary exacerbation and 1 = constipation/bloating)
- As per Table 10 in the Clinical Review by Dr. Gibril, 22 male and 14 female patients, between 18 and 53 years of age constituted the ITT patient population. All study patients were Caucasians. There was no major difference between treatment groups with respect to demographic characteristics. The mean age in the double-blind Creon®20 group was 23 y [males, = 55%; females, = 44%] while the mean age in the corresponding double-blind placebo group was as 24 y [males, = 66%; females, n = 33%].
- Test medication dosage (mean lipase units/kg/day) was calculated for each patient as the mean number of capsules taken per day multiplied by the lipase content per capsule (20,000 units) divided by the weight (kg) at the screening visit. As in the other CF trial and according to protocol, the dose was individualized for each patient while on a high fat diet. As shown in Table 11 of Dr. Gibril's Clinical Review, the mean dose of test medications were comparable across treatment groups in both the open-label and double-blind treatment phases. It is important to note that during open-label treatment, the mean dose for the Creon®20 group was 4907 [range 749 to 1227] lipase U/kg/day while the mean dose for the placebo group was 4782 [range 979 to 10096] lipase U/kg/day. During the double-blind treatment phase, the mean dose for the patients that were randomized to Creon®20 was 4537 [range 113 to 10542] lipase U/kg/day while for those that were randomized to placebo, the mean dose was 5107 [range 1007 to 12454] lipase U/kg/day. As per the other CF trial,

these figures were calculated from the number of capsules equivalent to the actual mean lipase.

- The duration of exposure to Creon®20 ranged from 10 to 36 days with a mean of 18 days for patients in open-label treatment. For double-blind treatment, the mean exposure to Creon®20 was 7 days [range 6 to 8 days]; the mean exposure to placebo was also 7 days.
- Using the mean CFA values as the primary efficacy analysis of efficacy, the results are as summarized in Table 9.

Table 9
Study S2233102
Changes in Coefficient of Fat Absorption (CFA)
ITT Study Population

	CFA (%)		Therapeutic gain	p-value[b]
	Placebo [n=18]	Creon®20 [n=18]		
Open-label (OL) treatment[a] Mean	88	89		
Double-blind (DB) treatment Mean	51	87		
Change from OL to DB treatment Mean	-37	-2	-35	**0.000**

This Table is based on Table 12 in Dr. Gibril's Clinical Review, with substantial modifications. The means have been rounded off, the ± SEM and the ranges have been deleted for simplification of presentation purposes.

a) All patients received Creon®20 capsules during open-label treatment, however, sample is broken down by double-blind treatment assignment for comparison

b) P-value calculated based on ANOVA model with factors for center, treatment, and center-by-treatment interaction.

- The mean CFA at the end of open label treatment phase was comparable between placebo (88%) and Creon®20 treated patients. It is worth noting that all patients in open-label phase were treated with Creon®20. 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 ANOVA method with center, treatment, and center-by-treatment interaction as model parameters. However, as pointed out in Dr. Chen's statistical review, the sponsor concluded that the ANOVA test also showed that the interaction between treatment and center was significant ($p = 0.07$) [The sponsor did not specify a significant level for treatment-by-center interaction test in the protocol]. In searching for an explanation for this finding, the sponsor indicated that the fecal fat excreted

by patient 60254 following double-blind placebo treatment exceeded the amount of dietary fat ingested. After excluding this outlier from the CFA analysis, a) the interaction of treatment-by-center was no longer significant (p = 0.26) and b) the CFA changes from the open-label to the double-blind phase between the treatment groups were still significant. The sponsor concluded that that the inclusion or exclusion of patient 60254 from the analysis did not alter the level of significance demonstrated in the treatment comparisons with regard to the mean change of CFA from the open-label to the double-blind phase of the trial.
[**NOTE**: In the MTL's opinion, the sponsor's explanation is plausible. On many occasions the amount of fat excreted in the stool could be higher than the amount of fat ingested. This extra fat may originate from at least three sources: desquamation of intestinal cells, bacterial synthesis (especially when bacterial overgrowth is present), and secretion of fat from intestinal cell to lumen. The sponsor conclusions were further validated by additional analyses carried out by Dr. Chen which included 1) ANCOVA analysis (also carried out by the sponsor who arrived at similar conclusions as Dr. Chen), 2) Change in CFA analysis by center, and 3) Subgroup analysis].

- As summarized in Table 13 of Dr. Gibril's clinical review, there was no significant difference between treatment groups in the mean change in daily fat intake from open-label to double-blind phase of the trial, i.e. 4.2 g/24 h and –5.5 g/24 h (p=0.294), respectively. These findings contrasted with the statistically significant difference between treatment groups in the mean change in daily fat excretion from open-label to the double-blind treatment phase, i.e. 62 g/24 h vs 2.3 g/24 h (p<0.001), respectively. The MTL concludes that, when taken in conjunction, all these findings demonstrate that the difference in CFA between Creon®20 and placebo is due to the difference in fecal excretion and not to the difference in fat intake. In other words, in Study S2233102 the difference between Creon®20 and placebo is as robust as that demonstrated in Study S2233101.
- As in Study S2233101, analysis of results of **secondary efficacy parameters** in Study S2233102 showed clear superiority of Creon®20 over placebo for stool frequency (p = 0.000), stool consistency (p = 0.001) and CGI, clinical global improvement (p < 0.001).
- Regarding Safety Evaluations, an increase in abdominal pain following double-blind placebo treatment was the largest treatment emergent difference seen between the groups: 9/18 (50%) patients that were randomized to placebo during the double-blind phase of the trial reported abdominal pain compared to 2/18 (11%) of those randomized to Creon®20. Also higher in the placebo than in the Creon®20 group was the use of antiflatulents. A comparison of change in physical examination from screening to termination showed 3/18 (16.7%) placebo patients experiencing abdominal tenderness or distension at termination, compared to 0/18 Creon®20 patients. There were no differences between the treatment arms in the frequency of other treatment emergent AEs. The types of events reported during the trial were not unexpected for patients with CF. No apparent treatment differences were detected on reports of markedly abnormal laboratories or vital signs.
  NOTE : The MTL agrees with the conclusion that, at the doses and experimental conditions used in Study S2233102, Creon®20 capsules are safe and also effective in controlling the symptoms of fat malabsorption in adult patients with cystic fibrosis.

B. CHRONIC PANCREATITIS

3. Protocol 223.2.01

- This double-blind, randomized, multi-center, placebo-controlled, 2-arm, parallel-group study was set to compare the effect of **Creon®10 (10,000 lipase units, USP)** with placebo in the control of steatorrhea, as assessed by the coefficient of fat absorption (CFA), in patients with **chronic pancreatitis** (CP). Secondary objectives were to investigate the effect of Creon®10 on stool fat, stool frequency and consistency, as well as clinical global improvement of disease symptoms (CGID). Also assessed were the safety and tolerance of Creon®10 capsules over a 4-week dosing period.
- The trial consisted of two consecutive two-week outpatient treatment phases. Patients entered a 2-week, single-blind, placebo run-in phase in which eligibility for the second phase was established. In the second phase, eligible patients were randomized to two weeks of double-blind treatment with either Creon®10 or placebo. Stools were collected for determination of fat content during the final 72-h 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 daily diet while on a high-fat diet, the number of stools and describe the consistency[33] of each stool. In addition, at each scheduled visit, patient and investigator independently evaluated the CGIDS using a 5-point rated scale[34].
- The study population consisted of patients with documented chronic pancreatitis and a history of steatorrhea requiring pancreatic enzyme supplementation. Details of entrance/reasons for exclusion criteria are given in Dr. Gibril's clinical review. The patients were to be recruited from ca. 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 trial to ensure that 54 would complete the double-blind phase.
- The following information on dose selection is worth to mention. During both the single blind-phase (placebo) and double-blind phase (placebo or Creon®10), patients were instructed to take the test medications orally according to the following dosing regimen: 4 capsules (40,000 lipase units) with meal plus two capsules (20,000 units) per snack. The sponsor indicated that these doses are consistent with customary clinical practice and the published literature suggesting that a minimum of 30,000 units of lipase must be delivered to the duodenum over a four-hour postprandial interval for adequate digestion of fat. Patients were instructed to take a minimum of 10 and a maximum of 24 capsules daily. Patients who took > 80% of study medication were considered evaluable.
- Assumptions on sample size were as follows. With 54 patients (27 per treatment arm), Type I error rate of 0.05, and a standard deviation of 18.23 (estimated from a previous trial), Study 223.2.01 was to have greater than 80% power to detect a difference of 15 in change from baseline CFA between Creon®10 and placebo.

[33] 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).

[34] The CGIDS was rated as 0 = **None** (symptoms not present); 1 = **mild** (symptom present but not bothersome); 2 = **moderate** (symptoms bothersome); 3 = **severe** (symptoms interfere with normal activities); and 4 = **incapacitating** (symptoms prevent patient from continuing normal activity).

- A total of 64 patients were enrolled in the single-blind placebo phase of the trial. Of the 64 enrolled, 27 patients (42.2%) entered the double-blind phase and completed the trial. These 27 patients [Creon®10, n = 13; placebo, n = 14] were evenly distributed across 16 centers. Of the total 27 patients, 9 were females, 8 males; 16 Caucasian, 10 Negroid; with a mean age of 51y in both treatment groups [range 31 to 74y]. The statistical procedures to assess efficacy and safety, are adequately described in Dr. Chen's Statistical Review and Evaluation.

NOTE: As noted by Dr. Gibril, in the original submission the sponsor did not provide an explanation on the 37 of the 64 patients that did not advance to the double-blind phase. Upon request, the following information was provided: 27/37 patients had a CFA > 80%; 7/37 failed inclusion criteria and 3/37 had other reasons.

RESULTS

- Analyses of demographic data showed no significant differences between the treatment groups for sex, race, age, height, and weight.
- Protocol deviations, mostly minor in nature, occurred in 14 patients. These deviations were evenly distributed between the two treatment groups.
- Mean dosage, calculated from the drug dispensed record was comparable between Creon®10 (12.5 capsules/day) and placebo (14.6 capsules/day). The mean duration of exposure to Creon®10 and placebo was 14.6 days and 15 days, respectively.
- Although the n for the ITT study population was 27, the sponsor included only 26 patients (Creon®10, n = 12; placebo, n = 14) in the efficacy analyses[35]. Summary results of CFA evaluations are given in Table 10.
- In the placebo group, the mean CFA during the single-blind placebo phase was 56%; this value increased by 12% (to 68%) during double-blind phase for those patients that were randomized to placebo. In those patients that were eventually randomized to Creon®10, the mean CFA during the single-blind placebo phase was 50%; this value increased by 36% (to 86%) during the double-blind phase where the patients received Creon®10 treatment. The sponsor concluded that the change in mean CFA from the single blind placebo phase (12%) to the double blind phase (36%) between treatments was statically different (p=0.019).
- Additional efficacy analyses were performed excluding Creon®10 patient #60109 whose fat excretion was greater than fat intake during the single-blind placebo phase. The sponsor stated that the change in the mean CFA remained significantly different between treatments (p=0.0226).
- From the above reported evaluations, the sponsor concluded that Creon®10 is effective in the treatment of fat maldigestion and steatorrhea secondary to pancreatic exocrine insufficiency in patients with chronic pancreatitis [see below for MTL concurrence with the sponsor's conclusion].

[35] Patient #60099 was excluded from the analysis due to missing data (lost stool collection) from the double-blind phase of the trial.

Table 10
Study 223.2.01
Changes in Coefficient of Fat Absorption (CFA)
ITT Study Population

	CFA (%)		Therapeutic gain	p-value
	Placebo [n=14]	Creon®10 [n=12]		
Single-blind placebo phase Mean	56	50		
Double blind phase Mean	68	87		
Change from single blind to double blind phase Mean	-12	-37	-25	**0.019**

- In addition to the above-summarized analyses, the sponsor performed the treatment efficacy comparison on the change in mean CFA from the single-blind placebo to the double-blind phase (the primary efficacy endpoint) using ANCOVA model with treatment and baseline (single-blind placebo phase) CFA as model variable/parameters. These results are summarized in Table 11. Also depicted in this Table are the changes in CFA in the ITT study population based on pre-stipulated protocol procedures. After excluding the Creon®10 patient with CFA value 122 from the analysis, the CFA change value for the Creon®10 group goes down from 37 to 28.5; the p-value of the 2-treatment comparison increases from 0.019 to 0.023. It is to be noted that the baseline CFA value for the excluded patient with CFA change value 122 was -33, indicating that the fecal fat excreted in the single-blind placebo phase exceeded the amount of dietary fat ingested. The following is to be considered. First, the p-value of the comparison Creon®10 to placebo (0.023) is **still statistically significant**. Secondly, and most importantly, it is biologically plausible to have fecal fat excretion exceeding the amount of dietary fat ingested. This **non-dietary fat** may originate from **desquamated intestinal cells** (a perfectly normal process), **secretion of fat from intestinal cell to lumen** (another perfectly normal process), and **synthesis of fat by intestinal bacteria** (an additional normal process that is exaggerated in patients with bacterial overgrowth).

- Based on the above considerations and the overall evidence at hand, the MTL concludes that data from Study Protocol 223.2.01 demonstrate that Creon®10 is effective in the treatment of fat maldigestion and steatorrhea secondary to exocrine pancreatic in sufficiency in patients with chronic pancreatitis.

Table 11
Study 223.2.01
Analysis Results on the CFA Change from Baseline to Double-blind Treatment Phase

	CFA %		p-value[a]
	Placebo	CREON®10	
I. Sponsor's original Analysis [*No patients excluded*]			
Single-blind Placebo Phase (OL)	[n = 14] **56**	[n = 12] **50**	
Double-Blind Treatment Phase (D-B)	[n = 14] **68**	[n = 12] **87**	
Change from OL to D-B	[n = 14] **12**	[n = 12] **37**	**= 0.019[b]**
II. Analysis with the Removal of one Outlier [*One Creon®10 patient with CFA change 122 excluded*]			
Single-blind Placebo Phase (OL)	[n = 14] **56**	[n = 11] **57.5**	
Double-blind Treatment Phase (D-B)	[n = 14] **68**	[n = 11] **86**	
Change from OL to D-B	[n = 14] **12**	[n = 11] **28.5**	**= 0.023[c]**

This Table is based on sponsor's information submitted in the Clinical Report, sub-section of 9.1, on pages 58 and 60 of volume 83.

C. Efficacy Conclusions

Using the change in coefficient of fat absorption (CFA) as the prospectively stipulated primary endpoint of efficacy, the data in NDA 20-725 demonstrate the Creon® is effective in the treatment of steatorrhea due to exocrine pancreatic insufficiency associated with cystic fibrosis and chronic pancreatitis. This conclusion is based on results of three well-designed and apparently well-executed randomized clinical trials: two [Studies S2233101 and S2233102] submitted in support of the cystic fibrosis indication and one [223.2.01] submitted in support of the chronic pancreatitis indication.

It is to be noted that the MTL conclusion on the cystic fibrosis indication is in agreement with the conclusion arrived at by Dr. F. Gibril (MO Review of NDA 20-725, September 15, 2003). However, Dr. Gibril believes that unlike the efficacy results in cystic fibrosis, the efficacy results in chronic pancreatitis patients did not demonstrate substantial evidence of efficacy. The MTL does not agree with this conclusion. As shown in Table 11 of the current review, the primary efficacy parameter (the change in coefficient of fat absorption from the open-label to the double-blind phase in pivotal Study 223.2.01), showed Creon®10 to be well differentiated from placebo. In this instance one pivotal study for chronic pancreatitis suffices because, based on the results of two critical trials, the drug has already been shown to be efficacious for the cystic fibrosis indication. Although the clinical manifestations may differ, chronic pancreatitis and cystic fibrosis are both examples of exocrine pancreatic insufficiency.

VI. Integrated Review of Safety

In addition to the NDA information, this review includes assessment of data from three Safety Updates:

Date of Safety Update	Period Covered
December 16, 2002	December 18, 1997 to September 30, 2001
July 9, 2003	September 30, 2001 to June 30, 2003
October 2, 2003	June 30, 2003 to present

- As summarized in the Clinical Review by Dr. Gibril, the sponsor analyzed safety data from 33 clinical trials involving a total of 1179 patients, with the following distribution:

FORMULATION	Number of Patients
Creon® Microspheres (Creon® MS),	924
Creon® Minimicrospheres (Creon MMS),	416
Creon®	1090[a]
Other pancreatic enzyme replacement therapy (PERT)	311
Placebo	369
Total Number of patients	1179[b]

a) Defined as patients in the Creon® plus those in the Creon® MMS group who took at least one dose of test medication.
b) This Total Number of Patients is higher than the Creon® patients (1090) because some of them participated in crossover trials and were counted twice.

- The majority of AEs were expected and most likely due to the underlying clinical conditions. In the Creon® group, a) the only AEs considered to be related to test medication reported in >1% of patients in the body system as a whole was abdominal pain [6%], occurring at an incidence comparable to placebo [also 6%] and b) diarrhea was reported as related to test medication in 2%, nausea in 1% and flatulence in 2% of patients. Again, all these incidences were similar to those seen with placebo. The one death that has occurred in these trials (Pt. 111, Protocol 223.8.01, Creon® group, US) assessed as not related to test medication (more details below). Based on the reported findings, the Medical Officer Reviewer concluded that, all in all, the use of the test medication in patients with steatorrhea due to EPI in CF or CP patients treated for 2 to 4 weeks is associated with an acceptable safety margin. The MTL agrees with this conclusion. However, because patients with EPI require life-long enzyme replacement therapy, long-term safety data are needed. This information is provided in the Post-marketing experience section of this review.
- Summary description of patient exposure is given in Table 11[36]. The following is worth noticing: The predominant exposure within the ISS was 2 to 4 weeks: 40% in the Creon® group, 68% in Creon® MMS, 41% in Creon® MS, 29% in placebo and 60% of those in the other PERT group. The next highest exposure was > 4 to 8 weeks (Creon MS 30%, Creon MMS 9%, placebo 8% and other PERT 5%). No patient in

[36] This Table corresponds to Table 8.8.1.2.1. in Dr. Gibril's review, with minor modifications.

either the Creon MMS group or placebo group was treated for more than 26 weeks; 30 patients in the Creon MS group were treated for more than one year.

Table 11
NDA 20-725
All Creon studies (n=33)
Scope of Investigations: Number of patients in ISS Database

Study design	Total patient	Creon MS	Creon MMS	Creon	Placebo	Other PERT
[n =]	1179	924	416	1090	369	311
DB, parallel	300	64	185	229	178	-
DB crossover	496	484	106	484	185	170
Open, crossover	302	296	125	297	-	123
Open, single-treatment	81	80	-	80	6	18

This Table is based on sponsor's Tables 8.8.3.1.1 and 8.8.4.2.1 (scanned, amended vol. 2, pages 491 and 497). Summary data on exposure and daily median lipase dose, are included as Appendix 1 in Dr. Gibril's review.

- The most common median lipase dose taken in all treatment groups was between 2,000 to 10,000 U/kg/day, with the following proportion of patients per group: total Creon, 48%; Creon MS, 48%; Creon MMS, 51%; and other PERT, 50%. of the patients. Ca. half of the patients in CF trials (47% to 55%) received a median lipase dose between 2,000 to 10,000 U/kg/day in all treatment groups while most CF children and adolescent were given more than 20,000 lipase U/kg/day. No CP patient took > 10,000 lipase/kg/day and all in all, adult patients, including those with CP, took a lower median total daily lipase dose than children.
- Methods and specific findings of safety review are detailed in Dr. Gibril's review. The 33 clinical trials which form part of the ISS included a variety of patients (CF, CP, post pancreatic and gastric surgery, and DM) and were conducted over an approximate 15 years period in the US, Europe, Australia, New Zealand and South Africa. In these trials, various formulations and strengths of Creon® MMS and MS were used. All formulations have been combined into the Creon® treatment group in the ISS Tables, as their basic ingredients are the same although the strength, pellet size, and capsule size may differ. The majority of patients were treated in crossover, double-blind design studies.
- Patient demographics at randomization for all Creon® studies are summarized in Table 8.8.2.1.1 of Dr. Gibril's review. Of the total 1179 patents participating in the 33 integrated Creon® trials, 677 (54%) had CF, 299 (25%) had CP, 94 (8%) were PS patients and 109 (9%) had DM. Of the 1090 patients exposed to Creon®, 924 received Creon® MS and 416 received Creon MMS. The majority of those receiving Creon were CF patients (62%), 25% were CP, 8% PS, and 5% were DM patients. Included among the 369 that were treated with placebo were 38 (10%) with CF, 258 (69%) with CP, 19(5%) with PS and 54(14%) with DM. The 311 patients in the other PERT group include 277(89%) with CF and 34(11%) with CP.
- Ca. half of the patients were 18 y or younger. This is consistent with the majority of patients being studied were CF patients with a mean age of 13, followed by CP patients with a mean age of 50 y .Overall, 30 patients were < 4 y old, 350 between 4 and 12 y and 45 were 60 y or older. The majority (65%) were Caucasian and 27% of unknown race (data not collected). All in all, more males (59%) than females (38%) were represented in the patient group. In CF patients the gender was 51% male, 43% female. and unknown in 6%, whereas in CP patients

there were more males (70%) than females (30%), which is representative of this disease group due to the higher representation of CP of alcoholic etiology. In summary, the demographic characteristics of the patients enrolled in the 33 integrated trials reflect the natural population of patients with CF and CP. Most studies were in CF patients with a mean age of 13 y.

- Administrative reasons accounted for the majority of the discontinuations, i.e. n=44 (3.7%) in all patients; these were primarily patients who failed to meet thew entry criteria after the run-in phase. In general, the completion of study rate was high in all Creon studies (>90%). The discontinuation rate due to AEs was small and was similar among the individual treatment groups.

Serious adverse events (SAEs)

- There was one death reported in the integrated studies:

> **Patient 111** (Protocol 223.8.01, Creon MS group, US) was a 11.7 y old M with CF. He had a history of pulmonary complications, Methicillin resistant Staph Aureaus (MRSA) and depression. The patient entered the study on (b) (6) began phase I Creon® treatment during the stabilization phase, and was randomized to Creon® 25,000 for the first treatment period of the cross over phase on day 9. He was admitted to the hospital with a four-day history of fever, chest pain, and productive cough with some shortness of breath. The patient developed an allergic reaction. He was placed on I.V. triple antibiotic therapy; respiratory therapy was also administered. MRSA grew from the central line culture and Pseudomonas sp. was isolated from the lung. The patient was discontinued from the trial because of his fever, chest pain, productive cough and shortness of breath at the end of Phase II day 20, and was placed on total parenteral nutrition. His condition continued to deteriorate, with increasing oxygen requirements for respiratory distress. Ten days later, the patient suffered cardiorespiratory arrest and died.
> The physician evaluated the event as not related to the test medication. Both the clinical reviewer and the MTL agree with this evaluation.

- Treatment Emergent SAEs[37] (including the above-summarized one case of death) occurred in 70 out of 1179 patients (5.9%), with a low incidence by body system. In controlled trials, the incidence of SAEs was 4.6% and comparable between Creon®, placebo and other PERT whereas in open-label studies, without an adequate comparator, the incidence was of SAEs was higher (20%). Although gender and race analyses for SAEs were carried out, these evaluations are inconclusive due to the small number of patients per cell and incomplete information.
- Ca. 764/1179 (65%) patients experienced at least one treatment-emergent adverse event (TESS), with incidence rates comparable among the groups: Creon® MS, 51%; Creon® MMS, 52%; other PERT, 46%; and placebo, 43%. The body systems most affected were the body as a whole (43%), digestive (29%), respiratory (23%) and the metabolic and nutritional system (9%). The four comparison groups sowed small numerical differences (25% to 34%) in the incidence of AEs in the body as a whole. Abdominal pain was the most common event in all treatment groups with the exception of headache in the Creon MMS group followed by abdominal pain.
- In the digestive system a total of 342/1179 (29%) patients reported TESS, with diarrhea being the most commonly observed AE (8%) and incidence rates comparable among the treatment groups.
- In the respiratory system, a total of 275/1179 (23%) patients reported TESS. These occurred with similar rates in the Creon® MS (17%) and the Creon® MMS (18%) groups, 6% in placebo and 14% in the other PERT group. Increased cough was the most commonly

[37] The are summarized in Dr. Gibril's review, Table 8.8.6.2.1.1 (scanned, amended volume 2, page 503); Appendix 3 in her review.

observed event in all patients (9%) followed by pharyngitis (5%). The sponsor indicated that respiratory events occurred primarily in the active treatment groups, which could reflect the higher number of CF patients in these treatment groups as compared to the placebo group, which was primarily composed of CP patients who would not be expected to suffer from respiratory events.

- **Intestinal obstruction** occurred in 2 patients: 1 (Patient 11, Protocol K22.5006) in the Creon® MS group; this patient had DIOS, a condition commonly found in CF patients); and 1 (Patient 2, protocol K2234.5010) in other PERT group. The latter patient experienced acute bowel obstruction while receiving Cotazyme-S-Forte.
- The incidence rates for TESS overall were slightly lower in the other PERT group and placebo groups compared to the Creon® group. The sponsor stated that there are no striking differences between the treatments in terms of incidence rates for TESS. The MTL agrees with this assessment.
- There were small numerical differences regarding the distribution of severe adverse events among between the treatment groups.
- All in all, TESS were considered unrelated to test medication in 42% of all patients, 40% of the Creon® MMS group, 32% of the Creon® MS group, 24% of the placebo group, and in 27% of the other PERT group. The relationship to test medication was assessed as unknown in 13% of all patients. In the Creon® group, the only TESS that was considered to be related to test medication in > 1% of the patients in the body as a whole was **abdominal pain** which occurred in 6% and was comparable to placebo with 6%. In the digestive system, Creon® group, diarrhea was reported as related to test medication in 2%, nausea in 1% and flatulence in 2% of patients. These incidencies were all similar to those in the placebo group. The sponsor concluded that there was no difference in terms of relationship to test medication that could be identified between (actually among) the treatment groups. The MTL agrees with this assessment.
- Due to the small number of patients per cell, the information on TESS by gender and race is not very helpful.
- The majority of laboratory parameters showed no clinically meaningful change from baseline either within or across treatment groups. Laboratory parameters that met the criteria for markedly abnormal were considered to reflect the underlying disease state or condition rather than a treatment effect. Except for the below-noted uric acid, the MTL agrees with this assessment on laboratories.

Changes in Urinary Uric Acid

- In her clinical review, Dr. Gibril identified **uric acid** as a laboratory value of clinical relevance for Creon®, due to the purine content of pancreatin. This concern applies especially to CF patients. Sponsor's Table 8.8.9.1.1 (Table 12 in the current review) displays urinary uric acid data from the 2 pivotal trials (S2233101 and S2233102) testing the efficacy and safety of Creon® MMS in CF patients[38]. The mean change in urinary uric acid from open-label to double-blind phase showed a decrease of 117mg/24h for placebo group which was significantly higher than the decrease of 26 mg/24 h occurring in patients in the Creon® group [p=0.024]. The sponsor stated that this finding supports that hyperuricosuria in patients

[38] Study participants who completed both open-label and double-blind 24-h urine collection were included in the analysis.

taking pancreatic enzyme supplements is related to purine content of pancreatic enzyme extracts. Accor4ding to Dr. Gibril's review, in the pivotal trials, 5/31 adults and 2/34 children/adolescent experienced **hyperuricosuria** (>800 mg/24 h) during open-label Creon® MMS treatment. During double blind Creon® MMS treatment, 3/31 adults and no child/adolescent had hyperuricosuria. No patients receiving double-blind placebo treatment had hyperuricosuria. The sponsor reported that L-T data on the persistence of hyperuricosuria and its impact on renal function are not available in these studies. In the meantime, if Creon® is approved, information on hyperuricosuria should be included in the labeling.

Table 12
NDA 20-725
Urinary Uric Acid (mg/24 h) in CF patients (Pivotal Trials S2233101 and S2233102)

	Open-label (OL) Creon® treatment		**Double-blind (D-B) treatment**		**Change from OL to D-B**	
	Placebo	**Creon®**	**Placebo**	**Creon®**	**Placebo**	**Creon®**
n	32	33	32	33	32	33
mean	543	563	427	537	-117	-26
p-value					**0.024**	

This Table corresponds to sponsor's Table 8.8.9.1.1 in the Clinical Report, with some modifications.

VIII. Dosing, Regimen, and Administration Issues

The sponsor's dosing used in the randomized clinical trials was different for the two indications that are being sought. A higher strength of test medication (Creon®20) was utilized in the CF trials in comparison to that used in the CP trial (Creon®10). This is an important issue to address. Nowadays, because of the possible occurrence of fibrosing colonopathy, particularly, although not exclusively, in young CF children, the advice is not to exceed a certain amount of daily enzymes, especially lipase. Some experts in the field claim that they give much larger daily amounts of enzymes to CP patients than those recommended for CF patients and that no cases of fibrosing colonopathy have been observed among their CP patients. However, to confirm the rule, at least one if not two cases of fibrosing colonopathy in patients with CP have now been published in the literature. One can therefore state that this disease (fibrosing colonopathy), already rare in PEP-treated CF patients, is even more rare among those CP patients treated with PEPs. Individualization of the amount of drug per patient has and continues to be the norm in the exocrine pancreatic deficiency and pancreatic enzyme supplementation area of the practice of medicine. Hence, in the clinical trials, the initial dose of enzymes was not specified. Patients were not instructed about maximum allowable dose per meal, snack, or day. In spite of these limitations, patients adjusted their own dose as guided by clinical symptoms and, in the final analysis, the doses taken by patients in both pivotal CF trials happened to fall within the dosage recommended by the CFFCC. Therefore, the MTL agrees with the clinical reviewer that the wording in the proposed package insert, in the Dosage and Administration section, is adequate and acceptable.

There are, however, additional issues some of them related to possible/realistic off-label use of the drug the MTL wishes to bring up. Part of this information was obtained by Dr. Marcelo Barreiro, a former GI Medical Officer, during an August 01, 2001 t-con with Dr.

Preston Campbell, Executive Director of the Cystic Fibrosis Foundation.

- The lowest age that PEPs are prescribed is at birth. Patients in whom the diagnosis is made by genetic testing pre-natally or who have meconium ileus at birth, are placed on PEPs within the first week of life. Half of the CF patients are diagnosed by 6 months of age. Loss of pancreatic function is a dynamic process. Patients with meconium ileus are born with complete pancreatic insufficiency.
- In answer to the question ***how do you give PEPs to babies?*** Dr. Campbell replied that to treat newborns the capsules are opened and the contents are sprinkled on the tongue, followed by some milk. To be given to older infants/children the PEPs are mixed with apple sauce or yogurt, but not in the milk bottle. It was noted that a pH of >6 may induce dissolution of the enteric coating of the microspheres and deliver the enzymes in the stomach. Ninety percent of enzymes are destroyed by gastric acid. It was also mentioned that milk can be used as a vehicle in patients fed through a gastrostomy tube.
- Anti-secretory medications are started at 3 months, more common by 6 months.
- Dr. Campbell was asked what are the most commonly used PEPs in CF patients. He responded that CF comprises about 50% of the PEP market. Of this 50%, by the end of 2000, Ultrase (ScandiPharm), Pancrease (Orth-Mc Neil), and Creon (Solvay), had ca. 25 to 30% of the market each. Organon Labs. Products had ca. 5%. All of the preparations are enteric coated, except Viokase (which nobody uses in CF patients) and Pancreatin.
- Although a liquid formulation would be nice, it is expected to loose >85% strength in the stomach.
- There is no pediatric formulation of PEs. Formulations containing 4,000 to 20,000 Units of lipase per tab/cap are considered "pediatric formulations".
- Finally, Dr. Campbell provided some comments on fibrosing colonopathy. CFF is finalizing an epidemiological study in those patients. There is a discrepancy between the European experience and that in the US. The occurrence of fibrosing colonopathy in Europe appears to be brand specific. Solvay products did not produce the disease. The investigator from the Netherlands who blamed Eudragit is serving time and the information was discarded. On the other hand, in the US experience, large doses of enzymes were used. It was noted that the enzymes lipase/protease/amylase are in a fixed ratio. When one increases the dose of lipase, the other two enzymes are also proportionally increased. In this country, some Pediatric gastroenterologists claim that 20,000 Unit tablets can give fibrosing colonopathy, but not two 10,000 Units tablets. But this is an empirical observation, never scientifically proven. There is the possibility that the cause of fibrosing colonopathy could be in the **protease concentration** of the tablet.
- In Dr. Campbell's opinion 5,000/kg/meal (snack) produces fibrosing colonopathy. This is the main reason why the CFF recommends to give their patients with CF doses of 2,000 to 2,500 Units/kg/meal (snack).
- The final recommendation from Dr. Campbell was not to allow pharmacies to substitute PEPs without physician's knowledge. He stated that there are generics of unproven quality and the use of these non-standardized preparations may lead to insufficient therapeutic affect or even to adverse events.

IX. Use in Special Populations

Although it is always important to address questions regarding use in special populations, cystic fibrosis and chronic pancreatitis are both orphan indications. The total number of cystic fibrosis patients that were exposed to Creon®20 in pivotal study S2233101 was 18 (Table 8). The total number of cystic fibrosis patients that were exposed to Creon®20 in pivotal study S2233102 was also 18 (Table 9). The total number of chronic pancreatitis patients that were exposed to Creon®10 in pivotal study was only 12 (Table 10). Due to this small number of patients per cell and other reasons, the MTL believes that evaluation of the use of the drug in special populations is not very helpful. It can be said, however, that Creon® is effective in certain pediatric populations since in pivotal Study S2233101 pediatric patients as young as 7 years of age and adolescents were randomized into the trial in which the drug was found to be safe and effective. Issues concerning off-label use in younger pediatric populations are addressed in Section VIII of the current review.

X. Conclusions and Recommendations

A. Conclusions

1. The sponsor of NDA 20-725 has presented evidence that orally administered **Creon®20** is safe and effective in the treatment of steatorrhea due to exocrine Pancreatic insufficiency in pediatric patients (>7 y of age), adolescents and adults with **cystic fibrosis.**

2. Convincing evidence has also been presented that orally administered **Creon®10** is safe and effective in the treatment of steatorrhea due to exocrine pancreatic insufficiency in adult patients with **chronic pancreatitis.**

Studies in both indications used the (adequate) **change in coefficient of fat absorption** (CFA) s the primary efficacy parameter. All in all, results of analyses of secondary parameters of efficacy were supportive of the conclusion arrived at with the primary efficacy parameter. Although, as noted above and below, there are major Chemistry deficiencies that need to be addressed, the MTL believes that the clinical data presented by the sponsor in NDA 20-725 are valid.[39]

B. Recommendations

1. NDA 20-725 is **approvable** for treatment of steatorrhea due to exocrine pancreatic insufficiency associated with 2 indications: a) cystic fibrosis; and b) chronic pancreatitis. This recommendation is based on results of three well-designed and apparently well-executed clinical trials: S2233101 and S2233102 for the cystic fibrosis indication and 223.2.01 for the chronic pancreatitis indication.

[39] The MTL does not agree with the Medical Reviewer statement on page 74, X. Conclusions and Recommendations, A. Conclusions, paragraph Number 5 that includes the following phrase: …"these clinical data may not be valid"…**The MTL believes that these clinical data are valid.**

2. To be approved the sponsor must address and resolve serious Chemistry deficiencies.
3. **There are no clinical deficiencies per se**, but the sponsor needs to link the intended to be marketed formulation with the formulation used in the clinical trials.
4. The deficiencies to be communicated to the sponsor, if any, are included at the end of the reviews of the corresponding disciplines.

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HFD-180

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/s/

Hugo Gallo Torres
10/2/03 01:25:14 PM
MEDICAL OFFICER