CLINICAL REVIEW

Application Type	NDA
Submission Number	20-725
Submission Code	AZ
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PDUFA Goal Date	20-December-2008
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Review Completion Date	30-April -2009
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

Table of Contents

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 $\geq$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)
*	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]

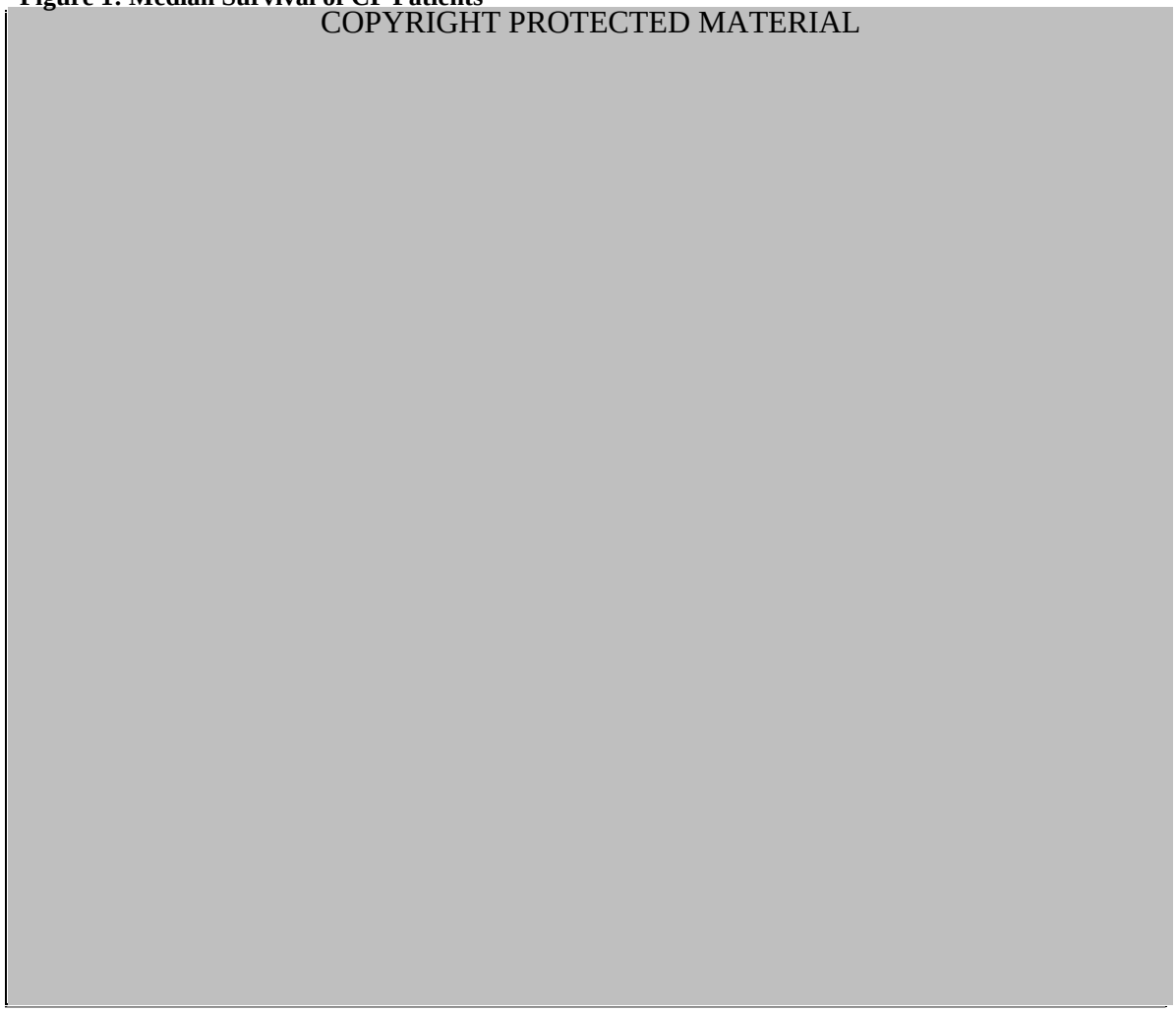
The 2004 FR notice also advised the public that FDA intended to exercise enforcement discretion until 28 April 2008. As the 2008 deadline approached, manufacturers expressed that they were not able to meet the original deadline. FDA determined that a substantial number of manufacturers who were otherwise 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 $\geq$30% difference in CFA in patients with severe EPI such as patients with Baseline CFA $\leq$40%. Therefore, this Reviewer will make a determination of efficacy based on demonstration of a $\geq$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 [$\leq$ or > 40%] was performed.

In the FAP, patients with Placebo CFA $\leq$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 ≤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*.

<u>Other references</u>

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 $\geq$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
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