CLINICAL REVIEW

Application Type	NDA
Submission Number	22-175
Submission Code	N
Letter Date	October 27, 2008
Stamp Date	October 27, 2008
PDUFA Goal Date	August 27, 2009
Reviewer Name	Marjorie F. Dannis, MD
Through	Anil Rajpal, MD
Review Completion Date	August 24, 2009
Established Name	Pancrelipase Delayed-Release Capsules
(Proposed) Trade Name	Pancrecarb
Therapeutic Class	Pancreatic Enzyme Product (PEP)
Applicant	Digestive Care, Inc.
Priority Designation	Standard
Formulation	For oral administration
Dosing Regimen	Not to exceed 2,500 USP lipase units/kg/meal or 10,000 USP lipase units/kg/day
Indication	Exocrine pancreatic insufficiency
Intended Population	Patients with exocrine pancreatic insufficiency

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This Reviewer recommends a Complete Response (CR) action based upon manufacturing and product deficiencies.

From a solely clinical perspective, the safety and efficacy of Pancrecarb MS-16 have been established for the treatment of patients with exocrine pancreatic insufficiency (EPI), ages (b) (4) to adult. The pivotal study 06-001 demonstrated the short-term efficacy and safety of

Pancrecarb MS-16 for patients with Cystic Fibrosis (CF) and EPI, ages eight years to adult. The Agency has determined that the extensive data from studies in the published literature with a variety of PEP formulations across pediatric age groups constitutes evidence of efficacy for PEPs in the pediatric population. Thus, in the opinion of this Reviewer, the clinical data submitted in the NDA are adequate to label the Pancrecarb MS-16 for patients with EPI from (b) (4) through adulthood.

1.2 Risk Benefit Assessment

The efficacy and safety of Pancrecarb MS-16 was demonstrated by the results of one short-term Phase 3 trial (Study 06-001). The pivotal study, 06-001, was a multicenter (US), randomized, double-blind, placebo-controlled, two-treatment, crossover study evaluating the efficacy and safety of Pancrecarb MS-16 in 24 patients, ages 8 to 43 years, with a confirmed diagnosis of CF and EPI. Efficacy was assessed by the comparison of the coefficient of fat absorption (CFA) following oral administration of Pancrecarb MS-16 and placebo. The results showed that there was a clinically meaningful and statistically significant increase in CFA in Pancrecarb MS-16 treated patients versus patients treated with placebo. In addition, the patients who were the most severely affected (had the lowest placebo CFA level), gained the most benefit by having the largest increase in CFA.

Exposure to Pancrecarb during many of the clinical studies was similar to what is currently encountered for PEP treatment of CF patients in clinical practice. Four deaths occurred during the Pancrecarb development program (all during the 2 year long term study), none of which was thought by investigators or by this Reviewer to be related to the study drug. The few (total of four) Serious Adverse Events (SAEs) were also thought by investigators and this Reviewer not to be related to Pancrecarb treatment. The Adverse Events (AEs) observed during the studies were consistent with the underlying diseases of the patients (mostly in the gastrointestinal and respiratory organ systems), and most were mild or moderate in severity. In general, the AE profiles reported in these studies was similar to the side-effect profiles of PEPs as reported in the medical literature.

PEPs are currently used by adult patients as well as pediatric patients as young as one month of age for the treatment of EPI due to a variety of causes. Although the clinical development program for Pancrecarb included patients as young as two years of age, the study that incorporated these younger patients (Study 091897) was performed using a different formulation of Pancrecarb (b) (4)). In addition, due to the design of this study (nonrandomized, uncontrolled, open label) and a primary endpoint chosen which was not "change in CFA", (b) (4) The pivotal study, 06-001, was the only study that established the efficacy and safety of Pancrecarb (only the MS-16 formulation) for patients with CF and EPI ages eight years or older.

The Division is not requesting that the Sponsor conduct any additional clinical trials to include patients younger than eight years of age. The Agency has decided that the existence of extensive data from studies in the published literature with a variety of PEP formulations across pediatric

age groups constitutes sufficient evidence of the efficacy for PEPs in the pediatric population. In addition, evidence of efficacy for Pancrecarb MS-16 for patients ages eight to adult was established in the pivotal trial. (b) (4) . The Sponsor is asked to submit a waiver for the age group of birth to 4 weeks.

Overall, the clinical information obtained from the short-term efficacy and safety studies is adequate to support approval of Pancrecarb MS-16.

1.3 Recommendations for Postmarketing Risk Management Activities

1.3.1 Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

In accordance with section 505-1 of the FDCA, a REMS is necessary for Pancrecarb Delayed-Release Capsules to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients.

The proposed REMS must include a **Medication Guide**: and a **Timetable for Submission of Assessments.** The timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. Each assessment must assess the extent to which the elements of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

1.3.2 Postmarketing Study Requirements (PMRs)

The Agency 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 taking Pancrecarb Delayed-Release Capsules.

Therefore, based on appropriate scientific data, the Agency has determined that, if this application is approved in a subsequent review cycle, pursuant to section 505(o)(3) of the FDCA, The following studies will be required:

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

(b) (4)

The specific details of these required postmarketing studies will be described more fully in the approval letter for this application, should it be approved.

1.3.3 Recommendations for other Postmarketing Study Commitments

Postmarketing Commitments will be negotiated should Pancrecarb receive an approval action during a subsequent review cycle.

2 Introduction and Regulatory Background

2.1 Product Information

Pancrecarb is the investigational agent studied in this application. Pancrecarb is a pancreatic enzyme product for oral administration. The delayed release capsules are bicarbonate-buffered and contain enteric-coated microspheres derived from porcine pancreatic enzymes. The active ingredient pancrelipase is a concentrated porcine extract comprised of the pancreatic enzymes lipase, amylase, and protease. Pancrecarb consists of pancrelipase formulated in (b) (4) dosage strengths: (b) (4) MS-8 (8,000 USP units of lipase), and MS-16 (16,000 USP units of lipase). The enteric coating is designed to facilitate the enzyme delivery into the duodenum.

The proposed trade name for this application is Pancrecarb. This name is currently under review.

The Sponsor is proposing that Pancrecarb receive the following indication:

> "Pancrecarb is a pancreatic enzyme preparation indicated for:
>
> Treatment of exocrine pancreatic insufficiency (EPI) associated with cystic fibrosis (CF), (b) (4)
>
> (b) (4)

The following is the Sponsor's proposed dosing regimen for meals:

- CF-Associated EPI: Begin therapy with 1,000 USP units of lipase/kg of body weight/meal in children less than 4 years of age, 500 lipase units/kg/meal (b) (4) in children 4 years and older, and adjust dosage according to symptoms to less than 2,500 units/kg/meal (b) (4) or less than 4,000 lipase units/g of fat per day. Infants may be given 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

(b) (4)

(b) (4)

The dosing regimen listed above for CF patients is consistent with the recommendations of the Cystic Fibrosis Foundation (CFF):

- 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. Total daily dose (3 meals plus 2 or 3 snacks) should not exceed 10,000 lipase units/kg/day.[1]

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are many PEPs being used in the US to treat EPI in adults and children, including neonates. PEPs were first marketed in the US in the 1920's prior to the Food Drug and Cosmetic Act of 1938 (the Act). The PEPs are widely available in the US and throughout the world as nutritional supplements, and as over-the-counter (OTC) and prescription therapies; however, in the US, PEPs were never evaluated for safety and efficacy under NDA until recently when the FDA required that all PEPs be marketed under an approved NDA by 2010. Cotazym (NDA 20-580) was approved in 1996, but is not currently marketed. On April 30, 2009, Creon (Pancrelipase) was approved (NDA 20-725) for the treatment of EPI due to CF or other conditions. Thus, Creon is the only currently marketed approved PEP.

2.3 Availability of Proposed Active Ingredient in the United States

Previously formulated Pancrecarb is currently marketed in the US and worldwide. The manufacturer does not have specific data on the number of patients treated with Pancrecarb. However, based on distribution data for the annual period of January 2007 through December 2007, approximately (b) (4) Pancrecarb capsules were shipped to wholesalers. If the usual range of daily intake of Pancrecarb is 10 to 20 capsules, this would represent approximately (b) (4) patients currently being treated with Pancrecarb on an annual basis.

In addition, the active ingredient in Pancrecarb, pancrelipase, is presently widely available from several different manufacturers as enteric coated (EC) and non-EC formulations (which are not

[1] Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol. 2006; 20(3):531-46. (PMID: 16782527)

interchangeable). Thus, many different PEP formulations are currently available in the United States and worldwide.
The availability of pancrelipase in the US may change in the near future. Secondary to concerns about variability in potency and safety of PEPs, the FDA is requiring that all PEPs be marketed under an approved NDA by April 28, 2010. Thus, PEPs will no longer be available without a prescription. Please see Section 2.5 for a complete description of regulatory history.

2.4 Important Safety Issues with Consideration to Related Drugs

PEPs were first marketed in the US prior to the Food Drug and Cosmetic Act of 1938; thus, they had never been evaluated for safety and efficacy under an NDA. In the 1990's, concerns about variability in potency and safety (such as fibrosing colonopathy) led to a series of regulatory decisions establishing that PEPs were not generally recognized as safe and effective (GRAS and GRAE, respectively). There were substantial irregularities in potency resulting in patients being both under dosed, as well as over dosed, each presenting a different safety and efficacy concern.

The most serious safety concern with PEP administration is fibrosing colonopathy (submucosal fibrosis). Fibrosing colonopathy (FC) is a condition that has been reported mainly in young children with CF who are being administered delayed-release PEP formulations. Although the exact etiology of FC is not known, studies have shown that the majority of the patients in whom FC developed were taking high dose PEPs.[2] There was also a concern that the enteric-coating or excipients in the delayed-release PEP formulations could lead to FC. As a result of these potential efficacy and safety concerns, the CFF and FDA published weight-based dosing guidelines for PEP administration (see section 2.1). Thus, monitoring for FC should be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products, as should the CFF/FDA weight-based dosing guidelines.

Hyperuricemia and hyperuricosuria have been reported in patients with EPI treated with PEPs. Caution should be exercised when prescribing PEPS to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This is the initial NDA submission for Pancrecarb. Relevant pre-submission regulatory activity for Pancrecarb was notable for the following:

A Special Protocol Assessment was submitted by the Sponsor on June 20, 2006. The protocol (No. 06-001) was entitled "A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Crossover Study to Evaluate the Effectiveness and Safety of Pancrecarb MS-16 (pancrelipase) in Reducing Steatorrhea in Children and Adults with Cystic Fibrosis. The Division and the Sponsor reached agreement on:

[2] FitzSimmons, SC, Burkhart, GA, Borowitz, D et al. High Dose Pancreatic-Enzyme Supplements and Fibrosing Colonopathy in Cystic Fibrosis. New England Journal of Medicine. May 1997; 336 Number 18; 1283-9.

The overall study design of the study which appeared to meet the criteria for demonstrating efficacy and safety set forth in the "Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs."

The dose stabilization period of 7 to 10 days appeared to be sufficient to qualify the subjects for the study.

The washout period of 7 to 10 days between the double-blind crossover treatment periods appeared to be sufficient in duration to reestablish baseline conditions.

The primary endpoint of comparison between active study drug and placebo in reduction of steatorrhea, as measured by change in percent coefficient of fat absorption (CFA), was acceptable. The CFA was to be calculated from the 72-hour stool collections and dietary records.

The patient population of CF patients was acceptable.

On February 5, 2007, the Division met with the Sponsor to discuss clinical and chemistry and manufacturing issues to satisfy requirements for NDA submission. The Sponsor believed that clinical studies (b) (4) Therefore, the Agency recommended that the Sponsor perform bioavailability studies with two dosage strengths of Pancrecarb (b) (4) Furthermore, if the Sponsor was unable to demonstrate comparability, they would need to provide adequate clinical efficacy and safety data for those strengths that were not shown to be comparable.

The regulatory background of the PEPs is as follows:

PEPs were first marketed in the US in the 1920's prior to the Food Drug and Cosmetic Act of 1938 (the Act). The PEPs are widely available in the US and throughout the world as nutritional supplements, and as OTC and prescription therapies; however, PEPs had never been evaluated for safety and efficacy under an NDA.

Due to concerns about variability in potency, the Agency published a Notice of Proposed Rule in the Federal Register (FR) on 15-July-1991 establishing that PEPs are not considered GRAS and GRAE, and the PEPs were considered misbranded. Concurrently, the Agency declared its intention to consider all PEPs to be new drugs requiring an approved NDA for continued marketing. This position was reaffirmed on 25-April-1995 with the publication of a Final Rule calling for all PEPs to be marketed drug products under approved NDAs in order to remain on

the market. In April 2004, the Agency published in the FR a Notice of Requirement for NDA Approval of all PEPs within the next four years, with a deadline of 28-April-2008. In October 2007, enforcement discretion was extended until 28-April-2010, but all PEPs must have an open IND by 28-April-2008, and an NDA submitted by 28-April-2009.

In April 2006, The Guidance for Industry; Exocrine Pancreatic Insufficiency Drug Products was published[3] (the Guidance). In this document, the FDA stated its expectation that animal-(porcine- and bovine-) derived PEP NDA applications would be submitted as 505(b)(2) applications. In these submissions, Sponsors were allowed to have a limited clinical development program, which could include short-term studies to establish efficacy and safety. These abbreviated clinical development programs are acceptable for PEP applications because assumptions were made about the efficacy and safety of these drugs based on a large body of efficacy and safety information available in the medical literature. The PEPs are also considered to be the standard of care for EPI due to CF and other causes, as described in the current CFF consensus statement.

2.6 Other Relevant Background Information

PEPs are currently used by adult patients as well as pediatric patients as young as one month of age for the treatment of EPI due to a variety of causes. Although the clinical development program for Pancrecarb included patients as young as two years of age, the study that incorporated these younger patients (Study 091897) was performed using a different formulation of Pancrecarb (b) (4) In addition, due to the design of this study (nonrandomized, uncontrolled, open label) and a primary endpoint chosen which was not "change in CFA", (b) (4) The pivotal study, 06-001, was the only study that established the efficacy and safety of Pancrecarb (only the MS-16 formulation) for patients with CF and EPI ages eight years or older.

The Division is not requesting that the Sponsor conduct any additional clinical trials to include patients younger than the age of eight. The Agency has decided that the existence of extensive data from studies in the published literature with a variety of PEP formulations across pediatric age groups constitutes sufficient evidence of the efficacy for PEPs in the entire pediatric population.

In addition, during a teleconference with the Sponsor on June 24, 2009, the Division stated that each of the (b) (4) Pancrecarb formulations differ from one another such that comparability of the (b) (4) formulations relative to one another had not been shown by the information provided in the NDA submission. Furthermore, additional clinical studies may be required to approve the (b) (4) MS-8 strengths. (b) (4)

[3] U.S. Department of Health and Human Services. Food and Drug Administration .Center for Drug Evaluation and Research (CDER). "Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products –Submitting NDAs."(http://www.fda.gov/Cder/guidance/6275fnl.pdf). April 2006.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the clinical information contained in this submission was acceptable.

3.2 Compliance with Good Clinical Practices

DSI inspections of selected clinical sites were performed, and included the inspection of Sites 007 in Cleveland, Ohio and 191 in Iowa City, Iowa (Drs. Strausbaugh and Ahrens respectively). These sites were selected by the Division based on the number of patients enrolled (Site 007 had 6 patients; Site 191 had 5 patients). In addition, Site 007 had the highest mean change in the coefficient of fat absorption (%CFA) and the highest number of treatment responders. The recommendation by DSI Investigator Roy Blay, Ph.D. is that "the data generated by the clinical sites of Drs. Strausbaugh and Ahrens appear acceptable in support of the respective application".

3.3 Financial Disclosures

Financial disclosure forms were reviewed. The Sponsor, Digestive Care Inc., states that they did not enter into a financial agreement with any of the clinical investigators which would affect the outcome of the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CMC data have been extensively reviewed by the Drug Product and Drug Substance Reviewers. A Complete Response Action is recommended. The Drug Product review states, "The data submitted in this application do not support the conclusion that the manufacture of pancrelipase is controlled, and leads to a product that is consistent and potent. Issues that preclude approval of this application include inadequate release and stability testing, inadequate process validation and inadequate stability data to support an assignment of expiry." Please see the CMC reviews for more detailed information.

4.2 Clinical Microbiology

According to Microbiology Reviewer, Vinayak Pawar, Ph.D., the drug product is a solid oral dosage form with microbial limit specifications and no microbiology deficiencies preventing approval which were identified. The reviewer did have the following comment to the Sponsor:

> "USP Chapter <1111> and the methods provided in Chapters <61> and <62> have been revised as of May 1, 2009. The acceptable limits for nonaqueous preparations for oral use are as follows:
>
> - Total Aerobic Microbial count = 10^3 CFU/g or mL which translates to a maximum acceptable count of 2000 CFUs.
> - Total acceptable combined yeast/molds count = 10^2 CFU/g or mL or 200 CFUs.
> - Absence of *Escherichia coli*.
>
> We recommend that you update your microbial limits requirement to the revised USP specifications."

Thus, NDA 22-175 was recommended for approval on the basis of a satisfactory product quality microbiology review. Please see the Microbiology Review for more detailed information on the microbiology data.

(b) (4) is the Drug Substance manufacturer for the Drug Product, Pancrecarb. A facility inspection took place during (b) (4) and revealed microbial contamination which could potentially be of clinical significance, especially to a chronically ill patient population such as CF patients. A consultation with Dr. Lorenz (Infectious Disease specialist of The Division of Anti-infective and Ophthalmology Products) revealed that although several types of microorganisms were present in the Drug Substance, these organisms are also typically found endogenously in the oral cavity, upper respiratory and gastrointestinal tracts of humans. Thus, their presence may not necessarily constitute a significant risk for most immunocompetent individuals. Dr. Lorenz recommended that since manufacturing levels exist for these particular organisms, the appropriate measures should be instituted to rectify the

contamination. In addition, he recommended the testing of the final product for microbial and toxin contamination; however, later discussion revealed that this would not be possible.

4.3 Preclinical Pharmacology/Toxicology

Since extensive human experience exists with the PEPs, and consistent with recommendations in the Guidance, no non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA. As outlined in the FDA Guidance for exocrine pancreatic insufficiency products, no toxicology studies were needed if excipients were classified as GRAS for oral administration or are USP/NF compendial excipients and are present at levels previously found acceptable. The sponsor did not conduct any nonclinical studies with Pancrecarb. All of the excipients used in Pancrecarb were USP/NF compendial items, and some were also GRAS and/or present at levels previously found to be acceptable. Please see the Nonclinical Pharmacology Review (by Tamal K. Chakraborti, Ph.D.) for more detailed information on the nonclinical information relevant to this NDA submission.

4.4 Clinical Pharmacology

Clinical pharmacology data have been reviewed by the Clinical Pharmacology Reviewer, PeiFan Bai, Ph.D. Her recommendation, from a clinical pharmacology perspective, is that the Pancrecarb application has the following deficiency:

"The submitted applesauce study (Protocol #080705) is deemed unacceptable since the assay method was not adequately validated. Therefore, we recommend that the sponsor repeat the applesauce study with a newly validated analytical method based on CMC's recommendation (a minimum of 5 data points for determination of assay linearity), and submit the results of the repeated applesauce study to FDA for review. The recommendation in the labeling with regard to the use of applesauce as a mixing medium to facilitate administration will be based on the review outcome. If the sponsor chooses not to repeat the applesauce stability study, there will be no recommendations with regard to the use of applesauce in the labeling."

Of note is that according to the ongoing internal discussions of DPG, (b) (4)

Please see Clinical Pharmacology Review for complete details.

4.4.1 Mechanism of Action

Pancrecarb acts locally in the gastrointestinal (GI) tract to improve the absorption of lipids, fat soluble vitamins, proteins, and to a lesser extent carbohydrates; it is not systemically absorbed.

4.4.2 Pharmacodynamics

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

4.4.3 Pharmacokinetics

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

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

There were a total of ten clinical studies (including one bioavailability) conducted in the Pancrecarb clinical development program; these clinical studies included a number of different designs (e.g., randomized, placebo-controlled, active-controlled, crossover, open-label). Duration of treatment in the trials also varied; the duration of treatment ranged from 7 days up to 2 years. The total number of patients enrolled in each study ranged from 6 to 106. See Table 1 for a listing and summary of these studies.

Table 1: Clinical Studies for Pancrecarb

Study Number	Design	Product	Primary Endpoint/Objective	No. of Pts / Age (Years)	Patient Population
06-001	Randomized, double-blind, placebo controlled, 2-way crossover	MS-16 and placebo	Change in CFA	21/ 8-43	CF
97-001-1B	Randomized, open-label, active controlled, 2-way cross-over	MS-8	Decrease lipase dose by 50% of MS-8 and comparator, compare CFA	19/ 12-27	CF
091897	Nonrandomized, uncontrolled, open label	MS-8	Weight gain	106/ 2-42	CF
97-001-2	Nonrandomized, open label, active controlled 1-way cross-over	MS-8	Change in CFA between usual dose and 50% reduced lipase dose Pancrecarb	6/ 4-17	CF
092100	Double blind, randomized, placebo -controlled, 2-way crossover	MS-8 and Placebo	Reduction in the frequency of diarrhea	13/ 28-55	HIV+ patients*
071503	Nonrandomized, open label, active controlled, 1-way cross-over	MS-16	Difference in mean doses/Determine lowest effective lipase dose	18/ 12-41	CF
2001-180	Nonrandomized, open label, active controlled, 1-way cross-over	MS-4	Compare CFA decrease lipase dose by 50% Given by G-tube	6/ 5-15	CF
092206	Open-label, placebo-controlled, bioavailability	MS-16 and placebo	Demonstrate the intestinal bioavailability of lipase, amylase and protease from MS-16 (single dose)	10 subjects enrolled Ages 36-79 years	Chronic Pancreatitis#
020296 (Study from 1996 with older formulation)	Double-blind, randomized, active-controlled, 2-way crossover	MS-8 low bicarb-onate	Differences in CFA between the two treatment periods	22/ 8-41	CF
111395 (Study from 1996 with older formulation)	Non-randomized, open-label, active-controlled, 1-way crossover	MS-8 low bicarb-onate	Differences in CFA between the two treatment periods	10/ 8-16	CF

* Experiencing HAART induced diarrhea that is successfully managed by pancrelipase therapy
# Documented alcohol-induced chronic pancreatitis or CF

5.2 Review Strategy

There were ten studies submitted with this NDA. They include one bioavailability study, two controlled clinical studies, one uncontrolled clinical study, and six supportive clinical studies. This review focuses on the two controlled clinical studies: the pivotal study (06-001) and study 97-001-1B. In addition, separate efficacy analyses were done for Study 97-001-2 (non-randomized, open label, active controlled, 1-way cross-over study using MS-8 formulation) and Study 2001-180 (nonrandomized, open label, active controlled, 1-way cross-over study using MS-4 formulation). There were two clinical studies (020296 and 111395) that were performed

using an older formulation of Pancrecarb. With the exception of inclusion in the general safety sections, the two studies with different formulations were not reviewed.

The majority of time was spent reviewing the pivotal study, 06-001. Efficacy of the MS-16 formulation of Pancrecarb was established from this randomized, double-blind, placebo-controlled study. Study 97-001-1B was a randomized, open-label, active-controlled, 2-way crossover study. The comparison between MS-8 and the reference pancreatic enzymes, at approximately 50% of their required dosages, failed to show superiority of Pancrecarb in improving CFA.

A pooled safety analysis was performed on all of the studies. Additionally, safety was assessed separately for Study 06-001 and Study 97-001-1B.

This NDA was submitted as a 505(b)(2) application. To obtain approval, PEP NDAs must meet the requirements for clinical studies described in 21 CFR 314.50. The Agency determined that there was a considerable body of evidence that replacement of pancreatic enzymes has clinical benefit for patients with cystic fibrosis and chronic pancreatitis (69 FR 23410). Thus, the limited clinical development program of Pancrecarb (one small pivotal study) was acceptable. However, the pivotal study used exclusively the MS-16 dosage strength and neither of the other two dosage strengths was adequately investigated. Thus, only the efficacy of Pancrecarb MS-16 was established.

5.3 Discussion of Individual Studies

5.3.1 Study 06-001

5.3.1.1 Study Design

The pivotal study, 06-001was a multicenter (US), randomized, double-blind, placebo-controlled, two-treatment, crossover study evaluating the efficacy and safety of Pancrecarb MS-16 in 24 patients, ages 8 to 43 years, with a confirmed diagnosis of Cystic Fibrosis (CF) and Exocrine Pancreatic Insufficiency (EPI). Efficacy was assessed by the comparison of the coefficient of fat absorption (CFA) following oral administration of Pancrecarb MS-16 and placebo. The study was conducted between February 13, 2007 and September 4, 2007.

The study consisted of 6 periods defined as: Screening Period which included a Screening Visit (Day -14 to -10), Dose Stabilization Period (-10 to 0 days), Treatment Period 1 (Days 1 and 2 at home; Days 3 to 6 in the General Clinical Research Center [GCRC]), Washout/Re-Stabilization Period (7 to 10 days), Treatment Period 2 (Days 1 and 2 at home, Days 3 to 6 in the GCRC) and the Follow-up Period which included End of the Study Visit (14 days following discharge at the end of Treatment Period 2)

Figure 1: Overall Study Design

- Screening Period
  - 4 days: Determine eligibility
- Open-label Dose Titration/Stabilization Period
  - 7-10 days: Pancrecarb
- **Treatment Period 1**
  - **6-8 days: Pancrecarb or Placebo**
- Washout/Re-stabilization Period
  - 7-10 days: Pancrecarb
- **Treatment Period 2**
  - **6-8 days: Pancrecarb or Placebo**
- Follow-up Period
  - 14 days after end of Treatment Period 2

5.3.1.2 Study Objectives

The primary objective of the study was to determine the efficacy and safety of Pancrecarb MS-16 versus placebo in reducing steatorrhea (as measured by 72-hour stool fat determinations) in children and adults with CF and EPI.

5.3.1.3 Patient Population

5.3.1.3.1 Key Inclusion Criteria

Patients were eligible for study participation if they were males or females seven years of age and older, and:

- Had confirmed diagnoses of CF – One or more clinical features consistent with CF *and* genotype consistent with CF or sweat chloride concentration > 60 mEq/L, and
- Had confirmed diagnosis of EPI - Currently receiving treatment with another PEP and documented fecal elastase < 100 micrograms/g stool.

5.3.1.3.2 Key Exclusion Criteria:

Patients were excluded from study participation if they had any of the following exclusion criteria:

- History of fibrosing colonopathy.
- History of solid organ transplant or major bowel surgery.
- History of being refractory to pancreatic enzyme replacement therapy (PERT)
- Had a condition known to increase fecal fat loss including: inflammatory bowel disease, celiac disease, Crohn's disease, tropical Sprue, Whipple's disease
- Had a current diagnosis or a history of distal intestinal obstruction syndrome (DIOS) in the past 6 months, or 2 or more episodes of DIOS in the past 12 months
- Poorly controlled diabetes or recent illness involving acute systemic administration of antibiotics within previous two weeks

5.3.1.4 Concomitant Medications

Patients were allowed to continue all usual CF medications and treatments, chronic oral azithromycin therapy, and inhaled antibiotic therapy. Study subjects could remain on a chronic regimen of systemic (oral or IV) antibiotics (except erythromycin) if they started the antibiotics at least 2 weeks prior to study screening, were at their usual bowel pattern at the time of screening, and did not stop or change these antibiotics during the study period. Concomitant administration of the following medications was prohibited during the study: drugs or products that affect fat absorption, including enemas, all laxatives including natural products (with exception of bisacodyl if required and prescribed by the investigator at any time during the study), mineral oil and castor oil, olestra (fat substitute), all fat blocking nutritional supplements, gastrointestinal motility modifiers, barium, potassium chloride, calcium carbonate, magnesium hydroxide, and enzymatic supplements.

5.3.1.5 Study Visits and Procedures

The majority of study visits were in the outpatient setting (study Visits 1, 2, 4, 6). During Visits 3 and 5, patients were hospitalized for four to six days wherein they were fed a controlled diet and were monitored. The two, 72-hour stool collections were performed during the inpatient stays for Visits 3 and 5. The study visits and procedures are summarized in Table 2 (electronically copied and reproduced from the Sponsor's submission).

Table 2: Schedule of Study Assessments

	Screening Period		Treatment Period 1							Washout/ Re-stabilization Period	Treatment Period 2							Follow-up Period
	Screening Visit 1 Day -14 to -10	Dose Stabilization Period Days -10 to 0	Visit 2	In-Home		In-Hospital – Visit 3				7-10 days	Visit 4	In-Home		In-Hospital – Visit 5				End of Study Visit 6 Day 14±3
			D 0	D1	D2	D3	D4	D5	D6 [+2]		D 0	D1	D2	D3	D4	D5	D6 [+2]	
Informed consent	X																	
Medical history	X																	
Complete physical exam	X					X								X				X
Abbreviated physical exam			X								X							
Height (cm)	X																	
Weight (kg)	X		X			X	X	X	X		X			X	X	X	X	X
Vital signs	X		X			X	X	X	X		X			X	X	X	X	X
Oximetry	X																	
Spirometry	X																	
Hematology	X								X								X	(X)[g]
Chemistry	X								X								X	(X)[g]
Urinalysis	X								X								X	(X)[g]
Spot urine (for uric acid / creatinine)	X								X								X	(X)[g]
Pregnancy test (urine)	X[a]		X[a]								X[a]							
Review of Inc/Exc Criteria	X		X[b]															
FE-1 test	X[c]																	

Table 2: Schedule of Study Assessments (cont.)

	Screening Period		Treatment Period 1							Washout/ Re-stabilization Period	Treatment Period 2							Follow-up Period
	Screening Visit 1 Day -14 to -10	Dose Stabilization Period Days -10 to 0	Visit 2	In-Home		In-Hospital – Visit 3				7-10 days	Visit 4	In-Home		In-Hospital - Visit 5				End of Study Visit 6 Day 14±3
			D 0	D1	D2	D3	D4	D5	D6 [+2]		D 0	D1	D2	D3	D4	D5	D6 [+2]	
Study subject diaries [d]		X	X	X	X					X	X	X	X					
Dietitian and RC instruction	X	X																
Phone follow-up		X		X	X					X		X	X					
High-fat diet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Open-labeled PANCRECARB® MS-16		X	X						X[h]	X	X						X[i]	X
Randomization			X															
Treatment Periods 1 and 2 active study drug or placebo				X	X	X	X	X	X[e]			X	X	X	X	X	X[e]	
Admit to GCRC						X	X	X	X					X	X	X	X	
Administer dye marker						X			X[f]					X			X[f]	
72-hour stool collection						X	X	X	X					X	X	X	X	
Food records						X	X	X	X					X	X	X	X	
Stool characteristics and frequency recording						X	X	X	X					X	X	X	X	
Adverse event reporting		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] For women of childbearing potential.
[b] Review of Inclusion/Exclusion Criteria (confirmed that the results of fecal elastase test met Inclusion Criteria).
[c] Fecal elastase performed on random stool sample.
[d] Diary was completed by study subject or parent (in the case of a minor) during the in-home portions of the study.
[e] Discontinued after the breakfast dose.
[f] If the first dye marker was not passed before the second dye marker was to be administered, the second dye marker was administered 96 hours after the first dye marker (Day 7).
[g] Repeated if results at the end of Treatment Period 2 were abnormal and clinically significant.
[h] Start previously established dose of PANCRECARB® MS-16 at the beginning of lunch.
[i] Start previously established dose of PANCRECARB® MS-16 or the subject's routine standard of care pancreatic enzyme treatment and usual diet at the beginning of lunch.

5.3.1.6 Randomization and Controls

The randomization was performed according to the [redacted] (b) (4) which described the generation of kit identifiers, emergency unblinding envelopes, and the kit distribution list. [redacted] (b) (4) a randomization list linking kit number to treatment sequence. Unblinded personnel in the DCI drug packaging group printed and applied the kit labels. Kit labels did not include any information that would reveal whether drug supplied for each treatment period was Pancrecarb MS-16 or placebo. Kit identifiers were prepared for the 2 age groups, ≥7 to 17 years and 18 years and older. As the patients enrolled into the study, the Clinical Project Manager assigned the next available kit from the appropriate age group of the kit distribution list.

Study drug (active study drug or placebo) for Treatment Period 1 and Treatment Period 2 was labeled with double-blinded investigational agent labeling. The label listed the name and address of the sponsor, protocol number, product storage information, a statement that it was "Active Study Drug or Matching Placebo", the required FDA investigational agent warning statement, a kit number and a bottle number. Each bottle was labeled with the treatment period for which it was to be used. Each bottle had a space for the study pharmacist or study coordinator to write in the study subject number and the date it was dispensed. Each bottle of study drug had 100 capsules of either active study drug or the matching placebo. All study site personnel were blinded to which product was used in each treatment period.

Enrollment of Additional Subjects

Twenty-nine subjects were enrolled in order to complete 20 evaluable subjects: 10 subjects ≥7 to 17 years of age (children) and 10 patients ≥18 years of age (adults). Patients who failed screening or who were randomized but withdrew prior to completion of Treatment Period 2 were replaced with a new subject.

In response to the Agency's Information Request (IR) regarding subject discontinuations, the sponsor clarified that three subjects discontinued and then two were enrolled as new patients following study screening and randomization procedures. Included in that response, the sponsor also indicated that there were three patients who had food intake records corrected after the database lock, which affected the primary efficacy assessments. The sponsor should have spontaneously informed the Agency regarding these details; however, the efficacy conclusion that Pancrecarb MS-16 increased CFA levels was still upheld.

The randomization was performed according to the (b) (4) which described the generation of kit identifiers, emergency unblinding envelopes, and the kit distribution list. (b) (4) prepared a randomization list linking kit number to treatment sequence. Unblinded personnel in the DCI drug packaging group printed and applied the kit labels. Kit labels did not include any information that would reveal whether drug supplied for each treatment period was Pancrecarb MS-16 or placebo. Kit identifiers were prepared for the 2 age groups, 7 to 17 years and 18 years and older. As the subjects enrolled into the study, the Clinical Project Manager assigned the next available kit from the appropriate age group of the kit distribution list. The DCI drug supply group then shipped the kit and emergency unblinding information to the study site.

5.3.1.7 Study Medication Dose Selection, Dispensing, and Compliance

The dose for each subject was selected during the Dose Stabilization Period. During this time period, a high-fat diet (approximately 2 gm fat/kg/day) was consumed. The patient's Pancrecarb MS-16 dose was managed in order to achieve control of pancreatic insufficiency symptoms and to achieve stabilized status according to the clinician's observations and subject's signs and symptoms. This chosen dose was used during the subsequent treatment periods.

Doses in this study were not to exceed a maximum lipase dose of 2500 lipase units/kg/meal, which is in agreement with the recommendation in the Guidance for Industry (FDA, 2006) of titration to less than 2500 lipase units/kg/meal.

Active study drug: Enteric-coated microspheres of pancrelipase, encapsulated in opaque gelatin capsules to mask its identity.

Placebo: Enteric-coated microspheres containing sodium starch glycolate and sucrose in place of pancrelipase, encapsulated in opaque gelatin capsules to mask identity.

Patients took all doses of study drug by mouth at the beginning of meals and snacks. The dose established during the Dose Stabilization Period was the dose used for the remainder of the study during Treatment Periods 1 and 2, and the Washout/Re-Stabilization Period.

An accurate and current accounting of the dispensing and return of study drug for each study patient was maintained on an ongoing basis by a research pharmacist. The amount of study drug dispensed and returned by the study subject was recorded on the Investigational Project Accountability Record. The study monitors verified these documents throughout the course of the study.

5.3.1.8 Efficacy and Endpoint Measures

5.3.1.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the comparison of the coefficient of fat absorption (CFA) after administration of Pancrecarb versus placebo. CFA was determined from the fat intake (calculated from the 72-hour dietary records) and fat excretion (from the 72-hour stool collection) during the efficacy evaluation period of each double-blind treatment period. Food intake was strictly controlled and recorded for 72 hours by qualified site personnel. The fecal fat measurements were obtained during a 72-hour in hospital stool collection. CFA was calculated as:

$$\frac{\textit{fat intake} - \textit{fat excretion}}{\textit{fat intake}} \times 100$$

The per-protocol population consisted of all study subjects who were randomized and completed both treatment periods with adequate 72-hour stool collections for analysis, with no major dosing protocol violations.

5.3.1.8.2 Secondary Endpoints

1. The coefficient of nitrogen absorption (CNA)
2. Stool frequency (number of bowel movements)
3. Stool weight

5.3.1.8.3 Safety Endpoints

Safety endpoints included assessments of or changes in frequency, duration, and severity of treatment-emergent AEs, clinical laboratory parameters, physical examination findings, and vital sign measurements in the safety population. The safety analysis population was defined as all patients who were randomized and received at least one dose of study drug.

5.3.1.9 Statistical Considerations

The primary endpoint comparison of CFA observed during treatment with placebo and during treatment with Pancrecarb was done using an analysis of variance appropriate for the crossover design. A *t* test for two independent samples was used to calculate power and sample size. An estimate of within-patient variance for calculating the effect size was not available; thus, the between-patient pooled variance was used instead.

According to Statistical reviewer, Freda W. Cooner, Ph.D.:
"The sample size was estimated based on mean treatment effect size of 30% in CFA difference between placebo and pancreatic enzyme and standard deviation of 41.2. The sponsor used normal approximation formula $N = (Z\alpha + Z_\beta)^2 \times (41.2)^2 / (30\%)^2$, where $Z\alpha = 1.96$ for 2-sided significance level of 0.05 and $Z_\beta = 1.28$ for 90% of power, to determine that 20 subjects were required for the primary comparison. According to the protocol (dated October 23, 2006), enrollment of 24 subjects would be sufficient to result in 20 evaluable subjects with 10 in each age group. However, as the result of subject discontinuations, it became necessary to enroll more than 24 subjects in order to complete 20 evaluable subjects. Therefore, the sponsor later indicated in the SAP (dated September 5, 2007) that "[t]he planned enrollment was up to 30 male or female subjects in order to complete 20 evaluable subjects…"

5.3.1.10 Protocol Amendments

According to the Sponsor, there were no amendments made to the protocol (dated 23 October 2006) or the Statistical Analysis Plan (SAP; dated 05 September 2007).

5.3.1.11 Study Results

5.3.1.11.1 Demographics

There were 29 patients between the ages of 8 and 43 years enrolled in Study 06-001. The mean age in children (≥ 7 to 17 years) was 12 years and in adults (≥ 18 years), 27 years. More males than females were enrolled in both age groups (children: 8 males, 3 females; adults: 10 males, 3 females). The patients were mostly homogeneous in terms of race with the majority of patients being Caucasian. Since CF is a disease predominantly of Caucasians, the study population is representative of the CF population. The demographics of patients enrolled in Study 06-001 are summarized below in Table 3.

Table 3: Demographics of Study 06-001

	Children < 18 (n=11)	Adults ≥ 18 (n=13)	Overall (n=24)
Age (years)			
Mean (SD)	12 (2.9)	27(7.4)	20(9.4)
Min-Max	8-17	18-43	8-43
Gender, n(%)			
Male	8 (73%)	10 (77%)	18 (75%)
Female	3 (27%)	3 (23%)	6 (25%)
Race, n(%)			
White	11 (100%)	11 (85%)	22 (92%)
Black	0 (0%)	2 (15%)	2 (8%)

5.3.1.11.2 Patient Disposition

Twenty-nine patients were enrolled in the Study 06-001. Of these 29 patients, 5 discontinued prior to randomization (screen failures) and 24 were randomized. Three patients discontinued the study (2 due to AEs and 1 protocol violation) and 21 subjects completed the study. A summary of patient disposition by age group is presented in Table 4 below.

Table 4: Patient Disposition

	Children n (%)	Adults n (%)	Overall n (%)
Enrolled	14 (100%)	15 (100%)	29 (100%)
Randomized *	11 (79%)	13 (87%)	24 (83%)
Completed Study	10 (71%)	11 (73%)	21 (72%)
Discontinued Study After Randomization	1 (7%)	2 (13%)	3 (10%)
Adverse Event	1 (7%)	1 (7%)	2 (7%)
Protocol Violation	0 (0%)	1 (7%)	1 (3%)
Per Protocol	9 (64%)	10 (67%)	19 (66%)

* Note: Patient took at least one dose study drug

There were five study sites with between four and nine patients enrolled at each site. Enrollment by site is summarized in Table 5.

Table 5: Patients per Study Site

Site Number	007	009	184	191	195
	007004	009004	184001	191005	195002
	007003	009003	184002	191004	195004
	007002	009001	184004	191003	195001
	007006	009002	184003	191002	195003
	007010	009006		191001	
	007001	009005		191006	
	007005				
	007009				
	007008				
Total Patients	**9**	**6**	**4**	**6**	**4**

5.3.1.11.3 Concomitant Medications

All study patients were to be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies. All concomitant medication and concurrent therapies were documented at the Screening Visit and at all study visits and at early termination when applicable. Dose, route, frequency of administration, and indication for administration, and dates of medication were captured.

5.3.1.11.4 Compliance with Study Medication

An accurate and current accounting of the dispensing and return of study drug for each study subject was maintained on an ongoing basis by a research pharmacist. The amount of study drug dispensed and returned by the study subject was recorded on the Investigational Project Accountability Record. The study monitors verified these documents throughout the course of the study.

Patient compliance with the study drug was determined in each of the two efficacy evaluation periods (Study Visit 2 and Study Visit 4) based on the review of the patient diary. Additionally, the study coordinator was in telephone contact with the patient on a daily basis to follow up with the patient on the high-fat diet compliance, active study drug or placebo compliance, and any AEs. At study's completion, the data obtained from patient diaries and from the research pharmacist were reconciled.

5.3.1.11.5 Dosing Information/Exposure

During the open-label Titration/Stabilization period and the open label Dose Re-stabilization Period 1, the mean dosage of study drug was approximately 1406 lipase units/kg/meal and 1557 lipase units/kg/meal respectively. Dosages were similar during both the double- blind treatment periods with a mean dose of 1565 lipase units/kg/meal.

One patient (184-002) had lipase doses over the protocol-specified maximum lipase dose of 2500 lipase units/kg/meal (Dose Stabilization 2799 lipase units/kg/meal; Wash-out/Re-Stabilization 2783 lipase units/kg/meal; and Double-blind treatment period 2720 lipase

units/kg/meal). At the Screening Visit, this subject's regimen was 88,000 lipase units/day consisting of 4 capsules of 20,000 lipase units and 1 capsule of 8,000 lipase units. Because this study only supplied the Pancrecarb MS-16 strength (16,000 units of lipase/capsule), if any rounding of doses was needed, the study subject was to be administered a lower starting dose. In error, the site rounded up and placed the subject on a 6 capsule/meal regimen, equivalent to 96,000 lipase units and 2720 lipase units/kg/meal, instead of 5 capsules/meal, equivalent to 80,000 lipase units, and 2266 lipase units/kg/meal. Despite the administration of this slightly (10%) higher than recommended dose, no gastrointestinal AEs were reported for this subject.

5.3.1.11.6 Protocol Deviations and Violations

A total of 33 protocol deviations occurred during this study. Two patients with deviations/violations were excluded from the Per Protocol analysis population, and one patient was excluded from the Completed Treatment analysis population. The protocol deviation/violations assessed by the Sponsor as major are tabulated below in Table 6.

Table 6: Major Protocol Deviation/Violations

Subject Number	Type of Deviation/Violation	Explanation	Timing of Deviation/Violation
009-003	Inclusion/Exclusion Criteria	Did not fulfill Exclusion Criteria, (abdominal surgery within the past 5 years). Had gastrostomy tube surgically removed secondary to excessive leak. A waiver was granted.	Prior to Screen Failure
195-001	Inclusion/Exclusion Criteria	Began dosing in Treatment Period 1 before the FE-1 results were available and Inclusion Criteria No. 4 confirmed (pancreatic insufficiency documented by spot FE-1 ≤ 100 µg/g stool at the time of randomization).	At Randomization
009-002	Dosing	Prior to confirmation of eligibility, the subject took dose of open-label drug in error. He returned the study drug to the site.	Prior to Screen Failure
184-002	Dosing	Received lipase doses over the protocol-specified maximum lipase dose of 2500 lipase units/kg/meal.	Post-Randomization Excluded from PP Population
191-002	Dosing	Given double-blinded drug instead of open-label drug at lunch at the GCRC at the end of Treatment Period 1. At discharge, the subject received the open-label study drug per protocol. Received 2 times the intended dose of double-blind medication at lunch on 2 occasions during Treatment Period 2.	Post-Randomization Excluded from PP population
191-005	Efficacy	Discarded part of the 72-hour stool collection in Treatment Period 1 (placebo).	Post-Randomization Excluded from PP population

5.3.1.11.7 Efficacy Results

5.3.1.11.7.1 Primary Efficacy Analysis

The primary endpoint in Study 06-001 was the change in the CFA in the efficacy population. The CFA measured during treatment with Pancrecarb was compared with the CFA measured

during treatment with placebo. Twenty-one patients who completed both double-blind treatment periods were included in the efficacy analysis population.

The Sponsor's results show that the mean CFA for patients receiving Pancrecarb was 82.5%; the mean CFA for patients receiving placebo (no treatment) was 46.3%. Therefore, the mean change in CFA was 36.2%. The efficacy results show a mean change in CFA that was statistically significant ($p < 0.001$). The FDA Statistician confirmed the results and was in agreement with the Sponsor. The results are summarized in Table 7 (electronically copied and reproduced from the Sponsor's submission).

Table 7: Comparison of Percent Coefficient of Fat Absorption (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
Overall (n = 21)	82.458	46.296	36.162[a]	27.781, 44.543
Children (n = 10)	80.841	45.834	35.007[a]	22.888, 47.127
Adults (n = 11)	84.075	46.758	37.317[a]	25.848, 48.786

[a] $P<0.001$

Source: 06-001 Study Report (Page 48, Section 11.1.1, Table 11-1)

The results of the primary endpoint show a statistically significant mean change in CFA in patients treated with Pancrecarb as compared to patients on placebo (no treatment). In the Pancrecarb clinical development program, the primary endpoint results were analyzed in conjunction with the changes in CFA for individual patients (see Section 5.3.1.11.6.2 below)

5.3.1.11.7.2 Additional Analyses of the Primary Endpoint

This Reviewer performed additional analyses of the primary endpoint, including analyses of the change in CFA by no-treatment (placebo) CFA, by treatment sequence, by gender, and by age.

Analysis by No-Treatment CFA

A widely accepted definition of severe EPI is patients who have a CFA less than or equal to 40% on no treatment. In addition, treatment effect has been reported to be more pronounced in patients with lower no-treatment CFA. . The medical literature notes that in the most severely affected patients an increase from baseline in CFA of 30% represents a clinically meaningful change, thus, this subgroup of patients was analyzed separately.

There were nine patients in the severe category. They had a mean placebo (no-treatment) CFA of 27% and a mean change in CFA on Pancrecarb of 51%. All but one of the most severely affected patients had an increase in CFA greater than or equal to 45%. Patient 195003 had an increase in CFA of 20%. This Reviewer looked for reasons to explain the apparent decreased efficacy for this particular patient relative to the other severely affected patients; however, no etiology was identified. Thus, in general, the most severely affected patients demonstrated the

greatest response to treatment with Pancrecarb. The magnitude of the change (mean change 51% in this group, and ≥45% in most of the patients) was a clinically meaningful result. Individual results for patients with CFA<40 on placebo are tabulated below in Table 8.

Table 8: Patients with Placebo CFA< 40

Patient Number	Placebo CFA	Pancrecarb CFA	Change CFA
009001	19	85	66
007002	19	71	52
007008	21	65	45
195003	24	44	20
195004	27	88	61
184003	30	92	62
007005	31	90	59
007001	36	82	46
191002	37	84	47

Mean change CFA (for Placebo CFA < 40 subgroup) = 51

For the subgroup of patients who had mild or moderate EPI (N=12) (defined by this Reviewer as a no-treatment CFA greater than 40), the mean change in CFA was 26%. The increase in CFA following Pancrecarb treatment (mean change in CFA of 26) was not as pronounced as seen in the patients with severe EPI. This result is not unexpected as these moderately affected patients have less of a capacity to respond, since they started at a higher no-treatment level. Individual results for patients with CFA<40 on placebo are tabulated below in Table 9. In general, there was a gradation in treatment responses with larger increases in CFA for patients with placebo CFAs at the low end, and smaller increases for higher placebo CFA levels.

Table 9: Patients with Placebo CFA>40

Patient Number	Placebo CFA	Pancrecarb CFA	Change CFA
191006	42	81	39
191004	48	78	30
195002	52	76	24
195001	52	90	38
184001	58	93	35
007010	58	91	33
007009	59	86	27
184004	63	97	34
009006	69	89	20
191003	71	79	8
184002	74	85	11
191001	78	90	12

Mean change CFA (for Placebo CFA> 40 subgroup) = 26

Overall, the additional efficacy analysis of change in CFA by no-treatment CFA in Study 06-001 showed that the increase in CFA on Pancrecarb treatment is greatest in the most severely

affected patients. The patients who had a higher no-treatment CFA showed smaller increases in CFA after treatment with Pancrecarb.

The inverse relationship between low no-treatment CFA and change in CFA (the lower the value initially, the higher the increase) is critical to the efficacy of the study. The mean change in CFA for all patients with a placebo CFA<40 was 51%; All of the patients (except patient 195003) who were the most severely affected (placebo CFA<40) gained the most benefit by having had an increase in CFA of at least 45%. This percentage increase was defined by the medical literature as a clinically meaningful result. Most other patients also had increases in CFA following treatment with Pancrecarb.

These results above support the approval of Pancrecarb for the treatment of EPI; treatment with Pancrecarb is beneficial to most patients. The treatment effect is variable; however, it follows a trend that the greatest change in CFA is observed in the patients with the lowest no-treatment CFA.

Analysis by Treatment Sequence

The efficacy results were analyzed according to sequence. Patients in sequence AB were randomized to receive Pancrecarb during the first treatment period followed by placebo during the cross-over treatment period. There were slightly more patients randomized to the AB sequence as opposed to the BA sequence (12 in sequence AB; 9 in sequence BA). The mean change in CFA was similar for patients in each sequence, 39% for sequence AB and 33% for sequence BA. The Statistical Reviewer also analyzed the efficacy results according to sequence and did not note any visible impact on efficacy outcomes. See Tables 10 and 11.

Table 10: Sequence AB Patients

Patient Number	Placebo CFA	Pancrecarb CFA	Change CFA
195003	24	44	20
195004	27	88	61
184003	30	92	62
007005	31	90	59
007001	36	82	46
191002	37	84	47
191006	42	81	39
195001	52	90	38
184001	58	93	35
007010	58	91	33
009006	70	90	20
191003	71	79	8
Mean	**45**	**84**	**39**

Table 11: Sequence BA Patients

Patient Number	Placebo CFA	Pancrecarb CFA	Change CFA
009001	19	85	66
007002	19	71	52
007008	21	65	45
191004	48	78	30
195002	52	76	24
007009	59	86	27
184004	63	97	34
184002	74	85	11
191001	78	90	12
Mean	**48**	**81**	**33**

The above analysis supports the fact that the order of treatment (placebo to Pancrecarb or Pancrecarb to placebo) did not affect the efficacy of Pancrecarb.

Analysis by Gender and Age

The efficacy results were also analyzed by gender and by age. The mean change in CFA was 39 in males vs. 29 in females; however, it was difficult to assess mean changes in CFA with respect to gender as there were three times as many males in the study as females (six females were included in the efficacy analysis population).

There were no meaningful differences in mean change in CFA with respect to age. A comparison between treatments within each age group (children vs. adults) was made and the results were similar to the overall analysis observed for both children and adults.

The primary efficacy endpoint was the comparison of the coefficient of fat absorption (CFA) after administration of Pancrecarb versus placebo. The overall results showed that a clinically meaningful and statistically significant increase in CFA was demonstrated in the efficacy analysis population, with an overall mean change in CFA of 36% ($p < 0.001$; 95% CI [-31.7, -19.3]). Unplanned additional and subgroup analyses showed that factors such as treatment sequence, gender, and age did not appear to affect efficacy; however, patients with lower placebo-treatment CFA tended to have a better response to treatment with Pancrecarb.

As expected from the published medical literature with treatment with other PEPs, the patients in this study who were the most severely affected (with the exception of one patient) gained the most benefit by having had an increase in CFA of at least 45%: this percentage increase was defined by the medical literature as a clinically meaningful result. Conversely, patients with higher placebo CFA had a lesser responses to Pancrecarb treatment.

5.3.1.11.7.3 Secondary Efficacy Analysis

There were several secondary efficacy endpoints in this study. These endpoints evaluated other factors that may help to support the results of the primary efficacy analysis; (b) (4)

(b) (4) The secondary efficacy endpoints analyzed had no clinically definable change that was clinically meaningful.

Coefficient of Nitrogen Absorption (CNA)

A major secondary endpoint was the comparison of CNA after administration of Pancrecarb versus placebo.

The results showed that the mean CNA for Pancrecarb and placebo were 79% and 47%, respectively. The mean change in CNA was 32%, and this was a statistically significant change. (See Table 12 electronically scanned and copied from Sponsor). These results were confirmed by the FDA Statistical Reviewer.

Table 12: Comparison of Percent Coefficient of Nitrogen Absorption (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
Overall (n = 21)	78.986	47.169	31.817[a]	26.102, 37.533
Children (n = 10)	78.440	43.810	34.630[a]	26.365, 42.895
Adults (n = 11)	79.532	50.528	29.005[a]	21.183, 36.826

[a] $P<0.001$

Source: 06-001 Study Report (Page 49, Section 11.1.1.2.1, Table11-3)

These results are supportive of a positive enzymatic effect of PEP treatment; however, a clinically meaningful change in CNA has not been established, so the clinical relevance of these results is not known.

Stool Frequency

Another secondary endpoint was the comparison of stool frequency (number of bowel movements) between Pancrecarb and placebo recorded over the 72-hour stool collection period. The overall results showed stool frequency was 6.1 bowel movements/72 hours for Pancrecarb versus 10.1 for placebo treatment. The difference of 4, a 39.6% decrease in stool frequency with Pancrecarb compared to placebo treatment was statistically significant ($P<0.001$). (See Table 13 electronically scanned and copied from Sponsor)

Table 13: Comparison of Stool Frequency (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
Overall (n = 21)	6.086	10.089	-4.004[a]	-5.607, -2.400
Children (n = 10)	5.591	9.409	-3.817[b]	-6.136, -1.499
Adults (n = 11)	6.580	10.770	-4.190[a]	-6.384, -1.995

[a] $P < 0.001$, [b] $P = 0.003$

Source: 06-001 Study Report (Page 50, Section 11.1.1.2.2, Table11-5)

Although statistically significant, the clinical significance of a four bowel movement difference over a 72 hour period is not clear.

Stool Weight

Another secondary endpoint was the comparison of stool weight between Pancrecarb and placebo recorded over the 72-hour stool collection period. The overall results showed stool weight was 655.9 g/72 hours for Pancrecarb versus 1308.5 for placebo treatment. The difference of a 652.6 gram decrease in stool weight with Pancrecarb compared to placebo treatment, was statistically significant ($P<0.001$). (See Table 14 electronically scanned and copied from Sponsor)

Table 14: Comparison of Stool Weight (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
Overall (n = 21)	655.939	1308.524	-652.585[a]	-813.369, -491.801
Children (n = 10)	507.129	1086.246	-579.117[a]	-811.610, -346.624
Adults (n = 11)	804.748	1530.802	-726.053[a]	-946.082, -506.024

[a] $P < 0.001$

Source: 06-001 Study Report (Page 51, Section 11.1.1.2.3, Table11-7)

Once again, the clinical significance of a 653 gram difference in stool weight over a 72 hour period is not clear.

These secondary efficacy variables were difficult to analyze accurately given the multiple variables involved and the nature of the underlying disease. Most secondary endpoints were subjective and assessed without using validated endpoint measures. Study 06-001 was of short duration and had a disproportionate amount of Pancrecarb treatment time, which made the analysis of treatment differences more difficult.

(b) (4)

5.3.1.11.8 Review of Safety

5.3.1.11.8.1 Deaths and Serious Adverse Events (SAEs)

There were no deaths reported during Study 06-001. There was one serious adverse event (SAE) reported by one patient, as follows:

Patient 184-002 was a 10-year-old Caucasian female who experienced an SAE of CF (verbatim term: acute exacerbation of CF) at the follow-up visit (Day 14) at the end of Treatment Period 2. The patient received Pancrecarb during Treatment Period 2. The SAE was treated with concomitant medication, although no new concomitant medication was prescribed. The SAE was assessed as resolved at an unscheduled visit to follow the SAE.

This event was assessed by the investigator to be probably secondary to the patient's underlying disease of Cystic Fibrosis, and was not attributed to treatment with study medication. This Reviewer is in agreement with the investigators' assessment.

5.3.1.11.8.2 Common Adverse Events

Of the 24 subjects randomized, 21 (87.5%) patients reported a total of 112 treatment-emergent adverse events (TEAEs). During Pancrecarb MS-16 treatment, 16 patients reported 47 TEAEs and during placebo treatment, 17 subjects reported 65 TEAEs. Ten of the 21 subjects reported TEAEs during both treatments.

There were no obvious differences in the types of AEs reported during either treatment period The most commonly reported AEs were in the gastrointestinal and respiratory systems as would be expected in this patient population. The most commonly reported AEs were abdominal pain, flatulence, abdominal distension, and headache. Two patients discontinued the study secondary to AE's; both patients were receiving placebo during this time. Patient 007-006 discontinued secondary to weight loss and patient 009-005 discontinued secondary to hyperglycemia and elevated liver function tests. One patient experienced an SAE (preferred term: CF; verbatim term: acute exacerbation of CF). The patient was receiving Pancrecarb MS-16 treatment when the SAE occurred.

Careful review of the adverse event datasets by this Reviewer did not reveal any obvious or noteworthy safety signals, and in general, the AE profile reported in this study is similar to the side-effect profile of PEPs as reported in the medical literature. See Table 15 below for a complete listing of the AEs reported in this study, (i.e., reported by 1 or more patients; $\geq$4% of patients).

Table 15: **Study 06-001, AEs observed during Treatment Period and Crossover Treatment Period**

System Organ Class	Preferred Term	Pancrecarb MS-16 N=21 (%)	Placebo N=24 (%)
Gastrointestinal disorders	Abdominal distension	2 (10)	4 (20)
	Abdominal pain	7 (33)	9 (38)
	Abnormal feces	1 (5)	0
	Constipation	0	0
	Diarrhea	2(10)	1 (4)
	Dyspepsia	2(10)	1(4)
	Flatulence	2(10)	5 (21)
	Frequent bowel movements	0	1 (4)
	Gastro esophageal reflux disease	1(5)	0
	Mouth hemorrhage	1(5)	0
	Nausea	1(5)	1 (4)
	Rectal tenesmus	0	1(4)
	Toothache	1(5)	0
	Vomiting	1(5)	2 (8)
Respiratory, thoracic and mediastinal disorders	Cough	2(10)	1(4)
	Nasal congestion	1(5)	2 (8)
	Pharyngeal erythema	1(5)	1(4)
	Pharyngo-laryngeal pain	1(5)	2 (8)
	Productive cough	0	1(4)
	Rales	1(5)	1(4)
	Rhinitis allergic	1(5)	0
	Sneezing	0	0
	Wheezing	1(5)	0
Nervous system disorders	Dizziness	0	1(4)
	Headache	2(10)	3 (13)
Investigations	Alanine aminotransferase increased	0	1(4)
	Aspartate aminotransferase increased	0	1(4)
	Blood glucose increased	0	1(4)
	Gamma-glutamyltransferase increased	0	1(4)
	Hemoglobin urine present	1(5)	0
	Sputum abnormal	0	1(4)
	Weight decreased	1(5)	2 (8)
Musculoskeletal and connective tissue disorders	Arthralgia	1(5)	0
	Back pain	1(5)	0
	Bone pain	0	1(4)
	Myalgia	0	1(4)
	Pain in extremity	0	1(4)
General disorders and administration site conditions	Chest pain	0	1(4)
	Pyrexia	0	1(4)
Hepatobiliary disorders	Hepatic steatosis	0	1(4)
Infections and infestations	Cellulitis	1(5)	0
Injury, poisoning and procedural complications	Thermal burn	0	0
Metabolism and nutrition disorders	Hypoglycemia	1(5)	0
Psychiatric disorders	Sleep disorder	0	0

Skin and subcutaneous tissue disorders	Rash	1(5)	0
	Urticaria	0	0
Surgical and medical procedures	Nasal sinus drainage	0	0
Vascular disorders	Hot flush	0	1(4)
Congenital, familial and genetic disorders	Cystic fibrosis	1(5)	0

5.3.1.11.8.3 Safety Summary

Exposure to Pancrecarb MS-16 (with average doses of about 1500 lipase units/kg/meal) during the study was similar to what is currently encountered for PEP treatment of CF patients in clinical practice. There were no deaths during Study 06-001and the one SAE reported during the study (exacerbation of CF) was assessed by the investigator to be related to the patient's underlying disease (CF). Two patients discontinued from the study due to AEs: one patient had weight loss and one patient had elevated LFT's. The weight loss was resolved at the follow-up visit; the LFT's were still mildly elevated at the follow-up visit. There were no other clinically significant abnormalities in laboratory data; individual patient vital signs and physical exams remained stable throughout the study.

The AEs observed during Study 06-001were consistent with the underlying disease of the patients (mostly in the gastrointestinal and respiratory organ systems), and most were mild or moderate in severity. The most commonly reported AEs were abdominal pain, flatulence, abdominal distension, and headache. Careful review of the adverse event datasets by this Reviewer did not reveal any obvious or noteworthy safety signals, and in general, the AE profile reported in this study is similar to the side-effect profile of PEPs as reported in the medical literature.

5.3.1.12 Summary and Conclusions for Study 06-001

The primary endpoint of the pivotal study, 06-001, was met. Treatment with Pancrecarb resulted in a statistically significant increase in absorption of fat (increase in CFA) compared to placebo. The most severely affected patients (placebo CFA <40%) demonstrated the greatest response to treatment with Pancrecarb (mean increase in CFA equal to 51), which was clinically meaningful. Subgroup analyses showed that factors such as treatment sequence and age did not appear to affect efficacy. The efficacy of Pancrecarb was demonstrated in adults and pediatric patients eight years or older.

Exposure to Pancrecarb during the study was within the range of what is currently encountered for PEP treatment of CF patients in clinical practice. The safety profile of Pancrecarb was acceptable and was consistent with the safety profile reported for other PEPs.

Thus overall, the results of the pivotal trial demonstrate that CF patients who are treated with Pancrecarb MS-16 have objective and subjective improvement of their clinical symptoms of EPI, and that Pancrecarb MS-16 is reasonably well tolerated by this patient population. These results support the approval of Pancrecarb MS-16 for the treatment of EPI in this patient population.

5.3.2 Study 97-001-B

5.3.2.1 Study Design

(b) (4) 97-001-1B, was a multicenter, randomized, open-label, active-controlled, two-way crossover study evaluating the efficacy and safety of Pancrecarb MS-8. This study, in 19 patients with a confirmed diagnosis of CF and EPI, was designed to compare measures of fat malabsorption before (while on usual PEP treatment) and after oral administration of Pancrecarb MS-8 at ~50% reduced lipase dose.

The study was carried out during two consecutive seven-day treatment periods in patients with CF. The dosage of Pancrecarb MS-8, the test pancreatic enzyme and the reference pancreatic enzymes [Creon® 20 (Solvay Pharmaceutical); Pancrease® MT-10 and MT-20 (Ortho/McNeil); Ultrase® MT-12, MT-18, and MT-20 (Axcan/Scandipharm)] were to be adjusted to ~50% of each patient's routine lipase dose requirement, but not lower than ~1,800 USP Units of lipase per gram of fat intake per day.

At the time of the screening visit, all patients were to have received pancreatic enzyme therapy in the form of Creon®, Pancrease®, or Ultrase®. The patients were then instructed to record their daily dietary intake and collect stools for three days on their regular enzyme dose. After determination of the current lipase dose, the existing enzyme therapy dose was reduced by ~50%, but not lower than ~1800 units of lipase per gram of fat intake per day. These reduced lipase doses were maintained throughout the study during each seven day treatment arm of the study. Following the first stool collection, the patients were instructed to collect stools for an additional three days on their reduced lipase dose. Only those patients with a coefficient of fecal fat excretion of no less than 15% (equivalent to CFA no more than 85%) during the initial ~50% reduced enzyme dose were randomly assigned in the two crossover treatment periods.

There were no wash-out periods between each of the two treatment periods; thus, patients remained on some PEP for the duration of the study.

5.3.2.2 Study Objectives

The objectives of this study were to determine the safety and efficacy of Pancrecarb at ~50% reduced lipase dose in reducing fecal fat and nitrogen losses in patients with cystic fibrosis when compared to other PEPs.

5.3.2.3 Patient Population

5.3.2.3.1 Key Inclusion Criteria

Patients were eligible for study participation if they were males or females greater than six years of age and:

- Had confirmed diagnoses of CF established by duplicate sweat chloride measurements greater than 60 mEq/L, using the method of Gibson and Cooke
- A coefficient of fecal fat excretion of ≥15% in the second outpatient stool collection using ~50% of usual enzyme dose

5.3.2.3.2 Key Exclusion Criteria

Patients were excluded from study participation if they had any of the following exclusion criteria:

- History of meconium ileus requiring surgical bowel resection.
- Receiving oral antibiotics or any drug known to interfere with fat digestion
- Participation in another concurrent clinical trial known to interfere with gastrointestinal motility and absorption of nutrients
- Patient is refractory to exogenous enzyme supplementation.

5.3.2.4 Concomitant Medications

It was the responsibility of the investigator to ensure that all changes in medication, or the commencement of medication during the study, were recorded in full in the case report form in a manner corresponding to the entries in the patient's medical records.

5.3.2.5 Study Visits and Procedures

The study visits and procedures are outlined below (electronically copied and reproduced from the sponsor's submission).

Days 1-3 (Home)
The following were recorded:
1. Drug Treatment
2. Food Records
3. Stool Description (number, consistency)
4. Adverse Events
5. Concomitant Medication

Days 4-7 General Clinical Research Center **(GCRC)**
Patients entered the GCRC the evening of the third day and were discharged after passing the second stool marker, usually on Day 7.
The following were recorded:
1. Drug Treatment
2. Weighing and Recording of Food Intake as outlined in Food Records
3. Stool Collection for Fecal Fat and Nitrogen using markers
4. Stool Description (number, consistency)
5. Adverse Events
6. Concomitant Medication
7. Nutritional Assessment

At the time of discharge, patients returned all unused medication and were dispensed the alternate enzyme product for Treatment Period 2.

Days 8-10 (Home)
1. Drug Treatment
2. Food Records
3. Stool Description (number, consistency)
4. Adverse Events
5. Concomitant Medication

Days 10-14 (GCRC)
Patients entered the GCRC the evening of Day 10 and were discharged after passing the second stool marker, usually on Day 14.
1. Drug Treatment
2. Determination of Fecal Fat and Nitrogen using markers
3. Weighing and Recording of Food Intake
4. Stool Description (number, consistency)
5. Physical Examination (Day 14)
6. Adverse Events
7. Concomitant Medication
8. Nutritional Assessment

5.3.2.6 Randomization and Controls

This study was a randomized, open-label, active-controlled, two-way crossover study. Patients were randomly assigned in the two crossover treatment period to receive either their usual enzyme dose at ~50% decrease lipase dose or Pancrecarb MS-8 at ~50% decreased lipase dose. No blinding procedures were used during the study.

5.3.2.7 Study Medication Dose Selection, Dispensing, and Compliance

At the time of the screening visit, all patients were to have received pancreatic enzyme therapy in the form of Pancrease, Creon, or Ultrase. After determination of the current lipase dose, the existing enzyme therapy dose was reduced by ~50%, but not lower than ~1800 units of lipase per gram of fat intake per day.

Only those patients with a coefficient of fecal fat excretion of ≥15% during the ~50% reduced enzyme dose (second stool collection) were admitted in the subsequent two treatment periods. Patients were then assigned randomly to one of two cross-over treatment sequences. The reduced lipase doses were maintained throughout the study on each seven-day treatment arm of the study. The patients either received a seven day supply of Pancrecarb or their usual pancrelipase product in the form of Pancrease, Creon, or Ultrase. A seven-day supply of enzyme capsules were dispensed and accounted for during the study period.

The investigator was to maintain accurate records of receipt of all test articles, including dates of receipt. In addition, records were kept regarding when and how much of each test article was dispensed to and used by each individual patient in the study. Reasons for departure from the expected dispensing regimen were recorded. A Drug Dispensing Form was provided for this

purpose. At the conclusion of the study, quantities of drug were reconciled with the dispensing documents, and the remaining drug was returned to the sponsor for accounting and disposition.

5.3.2.8 Efficacy and Endpoint Measures

The protocol did not identify any analysis population, yet two populations were used for analysis in the study report. An intent-to-treat (ITT) analysis was performed on the data collected from patients that were randomized to the study and completed both treatment phases. A per-protocol (PP) analysis was performed using the data from the repeat studies for patients 002, 003, and 009 at the Cincinnati site, and 004 and 009 at the Indianapolis site, and excluding patient 011 at the Indianapolis site.

5.3.2.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the comparison of the coefficient of fat absorption (CFA) after administration of Pancrecarb at ~50% reduced lipase dose as compared to usual PEP at ~50% reduced lipase dose. CFA was determined from the fat intake (calculated from the 72-hour dietary records) and fat excretion (from the 72-hour stool collection) during the efficacy evaluation period of each treatment period. The fecal fat measurements were obtained during a 72-hour in hospital stool collection. CFA was calculated as:

$$\frac{\textit{fat intake} - \textit{fat excretion}}{\textit{fat intake}} \times 100$$

5.3.2.8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoint was the percent of nitrogen malabsorption (CNA).

5.3.2.9 Statistical Considerations

As per Statistical Reviewer;
"There was no SAP during or after the clinical study. The final protocol specified that the primary outcome of percentage fat excreted would be compared between Pancrecarb MS-8 and the patient's usual EC enzyme using Grizzle's method for analyzing crossover studies. It is unclear what the sponsor meant by this Grizzle's method. Later in the study report, the sponsor indicated that a repeated measure ANOVA was used to assess treatment differences for each primary and secondary outcome variable and daily diary safety variables. The model was adjusted for study center, treatment period, treatment sequence, subject nested within sequence, and study center by treatment interaction. The sponsor further specified that PROC MIXED was used in SAS and treatment by center interaction term was removed due to its insignificance. With no missing data handling or multiplicity adjustment strategies proposed, the sponsor claimed that all variables were assessed at the two-sided 0.05 alpha level."

5.3.2.10 Protocol Amendments

Most of the protocol amendments were minor and did not impact the review, thus they will not be discussed.

5.3.2.11 Study Results

5.3.2.11.1 Patient Disposition, Demographic and Baseline Characteristics

Study 97-001-1B was conducted over approximately a four-year period from March 1997 to August 2001. Twenty-seven patients (Cincinnati site, 16; Indianapolis site, 11) were screened for study enrollment. Of the 27 patients, seven patients did not meet entry criteria and 20 patients (Cincinnati, 9; Indianapolis 11) were enrolled and randomized to treatment in the study. One patient (007) in the Cincinnati study center did not participate in the second arm treatment and was excluded from the efficacy analysis; thus 19 patients completed all study visits.

One patient from each site was enrolled with CFA greater than 85% and they were still included in the analyses. During the study, the investigators were allowed to repeat treatment assessments based on their judgments of whether a given treatment phase met protocol requirements. In three patients (002, 003, and 009) at the Cincinnati site, the investigators felt the Carmine red stool dye marker failed because of its color and so each had a repeat stool collection at their second treatment period. Two patients (004 and 009) at the Indianapolis site had repeat studies as outpatients based on the investigator's assessment of inadequacy of stool collections or possible lab error in specimen handling. The sponsor decided these repeat studies were not considered major protocol deviations although such a provision (i.e., to repeat studies based on the investigator's assessment that stool collection results are spurious) was not specified in the final protocol. One patient (011) at the Indianapolis site was non-compliant with the protocol specified diet and was identified by the sponsor as a major protocol violation.

While the protocol did not identify any analysis population, two populations were used for analysis in the study report. An intent-to-treat (ITT) analysis was performed on the data collected from patients that were randomized to the study and completed both treatment phases. A per-protocol (PP) analysis was performed using the data from the repeat studies for patients 002, 003, and 009 at the Cincinnati site, and 004 and 009 at the Indianapolis site, and excluding patient 011 at the Indianapolis site. The demographic variables are summarized in Table 16 below.

Table 16: Summary of Baseline Demographics (ITT Population)

	Cincinnati (n = 8)	Indianapolis (n = 11)	Overall [a] (n = 19)
Gender, n (%)			
Male	5 (62.5%)	4 (36.4%)	9 (47.4%)
Female	3 (37.5%)	7 (63.6%)	10 (52.6%)
Race, n (%)			
White	8 (100.0%)	10 (90.9%)	18 (94.7%)
Black	0 (0.0%)	1 (9.1%)	1 (5.3%)
Age (years)			
Mean (SD)	15.5 (3.2)	19.4 (4.4)	17.8 (4.3)
Min – Max	13.2 – 22.7	12.2 – 27.6	12.2 – 27.6
Weight (kg)			
Mean (SD)	52.8 (10.0)	58.6 (12.5)	56.2 (11.6)
Min – Max	37.0 – 69.9	29.8 – 82.3	29.8 – 82.3
Height (cm)			
Mean (SD)	159.9 (7.4)	163.8 (12.6)	162.2 (10.7)
Min – Max	148.2 – 172.0	135.8 – 182.0	135.8 – 182.0

[a] The results concur with those from the sponsor
Source: Statistical Reviewer's Table

5.3.2.11.2 Efficacy Results

5.3.2.11.2.1 Primary Efficacy Analysis

The following populations are defined for the purposes of the efficacy analysis:

- Intent-to-Treat (ITT) Population: defined as all patients randomized to the study and who completed both treatment phases.

- Per Protocol (PP) Population: defined as all patients that were randomized and completed the study without major protocol deviations. This analysis was performed using the data from the repeat studies for patients 002, 003, and 009 at the Cincinnati site and 004 and 009 at the Indianapolis site and excluding patient 011 at the Indianapolis site.

The ITT results, listed below in Table 17, showed (b) (4)

The Sponsor also used a PP population which showed (b) (4)

Table 17: Efficacy Results

	PANCRECARB® MS-8 Mean (SD)	Usual EC Enzyme Mean (SD)	P-value
ITT Population (n=19) CFA (%)	(b) (4)		
PP Population (n=18) CFA (%)			

Source: Adapted from Statistical Reviewer's Table (the results concur with those from the sponsor)

This reviewer performed an analysis of each individual's response to change in treatment (from Pancrecarb to placebo or vice versa). These results are shown below in Table 18, which represents the ITT population and Table 19, which represents the PP population. When analyzing the individual patient results, (b) (4)

Clinically, an individual patient may have improved symptoms of malabsorption (diarrhea, abdominal pain, flatulence) with increasing CFA values.

Table 18: Efficacy Results (CFA) Study 97-001-1B (ITT population)

(b) (4)

Table 19: Efficacy Results (CFA) Study 97-001-1B (PP population)

(b) (4)

The outcomes for the two populations were vastly different; statistical significance could be shown in the PP population but not the ITT population.

According to the statistical reviewer, this study lacked clinical trial rigidity; it was open-label, there was no washout period between two crossover treatment periods, there were repeated treatment assessments, there was a change of analysis plan, etc. Therefore, the efficacy results were not reliable (b) (4).

In addition, in each individual patient, the changes in CFA were not clinically meaningful. It is difficult to determine the clinical significance of CFA values that differ by (b) (4). (b) (4)

5.3.2.11.2.2 Additional Efficacy Analysis

Due to the poor study design and lack of clinical trial rigidity in Study 97-001-1B, no further efficacy analyses were performed.

5.3.2.11.2.3 Secondary Efficacy Analysis

The secondary efficacy endpoint was the comparison of CNA after administration of Pancrecarb MS-8 versus usual enzyme treatment.

In the ITT population, the results showed [redacted] (b) (4) In addition, since the clinical significance of CNA is not established, these secondary efficacy results are not clinically meaningful. (See Table 20 electronically scanned and adapted from Sponsor). These results were confirmed by the FDA Statistical Reviewer.

Table 20: Secondary Efficacy Results

	PANCRECARB® MS-8 Mean (SD)	Usual EC Enzyme Mean (SD)	P-value
ITT Population (n=19) CNA (%)	[redacted] (b) (4)		
PP Population (n=18) CNA (%)			

5.3.2.11.2.4 Efficacy Conclusions

While the supportive study, 97-001-1B, did not identify any analysis population, two populations were used for analysis in the study report, an ITT and PP population. The primary efficacy analyses for these two populations were vastly different; the ITT outcome was statistically significant, while the PP outcome was not. In addition, the individual changes in CFA observed per patient were not clinically meaningful.

According to the Statistical Reviewer, "Study 97-001-1B was an open-label, active-controlled, two-way crossover study without washout period and failed to show superiority of MS-8 in increasing CFA compared to the reference pancreatic enzymes, at approximately 50% of their required dosages. This study also had the potential for considerable bias because of inadequate trial design; [redacted] (b) (4)

[redacted] (b) (4)
.

5.3.2.11.3 Safety Results

5.3.2.11.3.1 Deaths and Serious Adverse Events (SAEs)

There were no deaths, serious adverse events or other significant AEs reported in Study 97-001-1B.

5.3.2.11.3.2 Common Adverse Events

During this open label, crossover study, 19 patients were randomized and received pre-determined doses of each study medication for 7 days as per protocol. Four patients received Pancrecarb MS-8 during a second 7 day period due to repeating the treatment phase. The mean doses of Pancrecarb MS-8 and usual enzyme taken during the study were both approximately 4,200 lipase units/kg/day.

During Study 97-001-1B, gastrointestinal signs and symptoms were recorded separately in patient diaries as opposed to collected as adverse events. The gastrointestinal signs and symptoms showed no significant differences in abdominal cramping/discomfort, bloating severity, flatulence/gas production severity and overall severity between the two treatments. (See Table 21 electronically scanned and copied from Sponsor.)

Table 21: Diary Data* (Mean ± SD) - ITT

	PANCRECARB® (n = 19)	Usual Pancrelipase (n = 19)
Number of Stools/Day	1.60 ± 0.5	1.43 ± 0.4
Abdominal Cramping/Discomfort	0.34 ± 0.4	0.24 ± 0.4
Bloating Severity	0.13 ± 0.3	0.22 ± 0.4
Flatulence/Gas Production Severity	0.27 ± 0.4	0.31 ± 0.4
Overall Severity	0.32 ± 0.4	0.31 ± 0.4

* None of the differences were statistically significant

With many of the complaints in the gastrointestinal category recorded separately from the other adverse events, there were not many adverse events recorded during Study 97-001-1B. Headache was the only adverse event which occurred in more than one person, 16 % in the Pancrecarb group and 21 % in the usual pancrelipase group. See Table 22 below for incidences of all AEs.

Table 22: Study 97-001-1B Summary of Adverse Events

Adverse Event	Pancrecarb n = 19 (%)	Usual Pancrelipase n = 19 (%)
Headache	3 (16)	4 (21)
Abdominal pain	1 (5)	0
Cold symptoms	1 (5)	0
Constipation	0	1 (5)
Increased sinuses congestion	1 (5)	0
Menstrual cramps	0	1 (5)
Rash	1 (5)	0
Stuffy nose	1 (5)	0
Temp >37.5	1 (5)	1 (5)
Tooth extraction	1 (5)	0

5.3.2.11.3.3 Safety Summary

Exposure to Pancrecarb (with dosages of approximately 4,200 lipase units/kg/day) during the study was similar (although may be slightly less) to what is currently encountered for PEP treatment in CF patients in clinical practice. There were no deaths, serious adverse events or other significant AEs reported in Study 97-001- 1B. There were no cases of fibrosing colonopathy. The only laboratory evaluation performed was fecal fat and fecal nitrogen analyses in stool samples.

Patients reported abdominal discomfort/distension, bloating and flatulence with equal severity in the Pancrecarb and usual pancrelipase treatment groups. These complaints are typical for this patient population of CF patients with EPI. Individual patient vital signs and physical exams remained stable throughout the study.

Therefore, treatment with Pancrecarb appeared to be well tolerated. The safety profile was consistent with that of other PEPs reported in the literature. However, the open-label study design may have introduced bias in the study, so the specific safety information (although minimal) attained from Study 97-001-1B may not be reliable data.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The sponsor is proposing that Pancrecarb receive the following indication:

Pancrecarb is a pancreatic enzyme preparation indicated for:

- Treatment of exocrine pancreatic insufficiency (EPI) associated with cystic fibrosis (CF), (b) (4)

Since this application is recommended to receive a CR action, specific wording for labeling of Pancrecarb was not negotiated during this review cycle; however, in the opinion of this Reviewer, the data submitted to the Pancrecarb application support the general statement that Pancrecarb is indicated for the treatment of (b) (4) EPI secondary to a variety of causes, including CF (b) (4) It is noted that all of the patients enrolled in the clinical studies submitted to the NDA had EPI due to cystic fibrosis, except one study which had a population of HIV+ (Human Immunodeficiency virus) patients with HAART induced diarrhea.

(b) (4)

6.1.1 Methods

The efficacy evaluation of the Pancrecarb clinical program involved review of several studies. The pivotal study, 06-001, submitted for this NDA used only the MS-16 dosage strength during the clinical trial. Since the other dosage strengths (MS-4 and MS-8) were not shown to be comparable to the MS-16 dosage strength, this reviewer also reviewed the efficacy data from several supportive clinical trials. These were Study 97-001-2 (a nonrandomized, open label, active controlled, 1-way, cross-over study of 50% decreased dose of MS-8) and Study 2001-180 (nonrandomized, open label, active controlled, 1-way, cross-over study using MS-4 given by gastrostomy tube at 50% decreased dose). The studies will be discussed separately as the differences in study design do not allow for the pooling of data. The two controlled clinical studies 06-001 and 97-001B are reviewed in detail (see Section 5.3 for a detailed review of each of these studies).

As described in published consensus documents (e.g., Borowitz DS, Grand RJ, Durie PR, et al., J Pediatrics, Nov 1995), decreased CFA is an accepted indicator of EPI, and an increase in CFA is associated with enhanced pediatric growth and development. Thus, the change in CFA can be used as a reasonable marker for pancreatic enzyme activity. A clinically meaningful increase in CFA in CF patients is accepted to be an increase of 30% or greater in the most severely affected patients (i.e., those patients who have baseline CFA less than 40%). There is no accepted clinically meaningful increase in CFA that has been determined for patients with EPI due to causes other than CF; however, as EPI due to any cause has similar clinical findings, it would be reasonable to consider this degree of change as meaningful in EPI due to pancreatectomy and chronic pancreatitis. In addition, there is no accepted change in CFA that has been shown to be clinically meaningful in patients with a Baseline CFA greater than 40%. Patients with higher CFAs at baseline tend to have smaller increases in CFA with PEP administration, as these patients have a lesser capacity to respond. Therefore, and in concert with the Agency's "Guidance for Industry Exocrine Pancreatic Drug Products – Submitting NDAs", the Division accepts the use of CFA as the primary efficacy measure in the pivotal study, 06-001, as reasonable and appropriate.

6.1.2 Demographics

The entire clinical development plan for Pancrecarb included patients ages two years to adulthood; however, some of the studies with younger pediatric patients were not robust enough for conclusions to be drawn regarding efficacy and safety based only on those studies.

6.1.2.1 Pivotal Study: 06-001

There were 29 patients between the ages of 8 and 43 years enrolled in Study 06-001. The mean age of children (≥ 7 to 17 years) was 12 years and the mean age of adults (≥ 18 years) was 27 years. More males than females were enrolled in both age groups (children: 8 males, 3 females; adults: 10 males, 3 females). The patients were mostly homogeneous in terms of race with the majority of patients being Caucasian. Since CF is a disease predominantly of

Caucasians, the study population is representative of the CF population. The demographics of patients enrolled in Study 06-001 are summarized below in Table 23.

Table 23: Demographics of Study 06-001

	Children < 18 (n=11)	**Adults ≥ 18 (n=13)**	**Overall (n=24)**
Age (years)			
Mean (SD)	12 (2.9)	27 (7.4)	20 (9.4)
Min-Max	8-17	18-43	8-43
Gender, n(%)			
Male	8 (73%)	10 (77%)	18 (75%)
Female	3 (27%)	3 (23%)	6 (25%)
Race, n(%)			
White	11 (100%)	11 (85%)	22 (92%)
Black	0 (0%)	2 (15%)	2 (8%)

6.1.2.2 Study 97-001-1B

There were 19 patients between the ages of 12 and 28 years enrolled in Study 97-001-1B. The mean age was 18 years; there were approximately equal numbers of males and females. Once again, the patients were mostly homogeneous in terms of race with the majority of patients being Caucasian, which is representative of the CF population. The demographics of patients enrolled in Study 97-001-1B are summarized below in Table 24.

Table 24: Summary of Baseline Demographics (ITT Population)

	Cincinnati (n = 8)	**Indianapolis (n = 11)**	**Overall [a] (n = 19)**
Gender, n (%)			
Male	5 (62.5%)	4 (36.4%)	9 (47.4%)
Female	3 (37.5%)	7 (63.6%)	10 (52.6%)
Race, n (%)			
White	8 (100.0%)	10 (90.9%)	18 (94.7%)
Black	0 (0.0%)	1 (9.1%)	1 (5.3%)
Age (years)			
Mean (SD)	15.5 (3.2)	19.4 (4.4)	17.8 (4.3)
Min – Max	13.2 – 22.7	12.2 – 27.6	12.2 – 27.6

[a] The results concur with those from the Sponsor
Source: Adapted from Statistical Reviewer's Table

6.1.3 Patient Disposition

6.1.3.1 Pivotal Study 06-001

Twenty-nine patients were enrolled in the Study 06-001. Of these 29 patients, 5 discontinued prior to randomization (screen failures) and 24 were randomized. Three patients discontinued the study (2 due to AEs and 1 protocol violation) and 21 patients completed the study. A summary of patient disposition by age group is presented in Table 25 below.

Table 25: Study 06-001 Patient Disposition

	Children n (%)	**Adults n (%)**	**Overall n (%)**
Enrolled	14 (100%)	15 (100%)	29 (100%)
Randomized *	11 (79%)	13 (87%)	24 (83%)
Completed Study	10 (71%)	11 (73%)	21 (72%)
Discontinued Study After Randomization	1 (7%)	2 (13%)	3 (10%)
Adverse Event	1 (7%)	1 (7%)	2 (7%)
Protocol Violation	0 (0%)	1 (7%)	1 (3%)
Per Protocol	9 (64%)	10 (67%)	19 (66%)

* Note: Patient took at least one dose study drug

There were five study sites with between four and nine patients enrolled at each site. Enrollment by site is summarized in Table 26.

Table 26: Study 06-001 Patients per Study Site

Site Number	**007**	**009**	**184**	**191**	**195**
	007004	009004	184001	191005	195002
	007003	009003	184002	191004	195004
	007002	009001	184004	191003	195001
	007006	009002	184003	191002	195003
	007010	009006		191001	
	007001	009005		191006	
	007005				
	007009				
	007008				
Total Patients	**9**	**6**	**4**	**6**	**4**

6.1.3.2 Study 97-001-1B

Study 97-001-1B was conducted over approximately a four-year period from March 1997 to August 2001. Twenty-seven patients (Cincinnati site, 16; Indianapolis site, 11) were screened for study enrollment. Of the 27 patients, seven patients did not meet entry criteria and 20 patients (Cincinnati, 9; Indianapolis 11) were enrolled and randomized to treatment in the study. One patient (007) in the Cincinnati study center did not participate in the second arm treatment and was excluded from the efficacy analysis; thus 19 patients completed all study visits.

One patient from each site was enrolled with CFA greater than 85% and they were still included in the analyses. During the study, the investigators were allowed to repeat treatment assessments based on their judgments whether a given treatment phase met protocol requirements. In three patients (002, 003, and 009) at the Cincinnati site, the investigators felt the Carmine red stool dye marker failed because of its color and so each had a repeat stool collection at their second treatment period. Two patients (004 and 009) at the Indianapolis site had repeat studies as outpatients based on the investigators assessment of inadequacy of stool collections or possible lab error in specimen handling. The sponsor decided these repeat studies were not considered major protocol deviations although such a provision (i.e., to repeat studies based on the investigator's assessment that stool collection results are spurious) was not specified in the final protocol. One patient (011) at the Indianapolis site was non-compliant with the protocol specified diet and was identified by the sponsor as a major protocol violation.

While the protocol did not identify any analysis population, two populations were used for analysis in the study report. An intent-to-treat (ITT) analysis was performed on the data collected from patients that were randomized to the study and completed both treatment phases. A per-protocol (PP) analysis was performed using the data from the repeat studies for patients 002, 003, and 009 at the Cincinnati site, and 004 and 009 at the Indianapolis site, and excluding patient 011 at the Indianapolis site.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for 06-001 was to compare the coefficient of fat absorption (CFA) following oral administration of Pancrecarb and placebo or the "change in CFA". The fecal fat measurements were obtained during a 72-hour in-hospital stool collection. The pre-specified mean change in CFA of 28.6% was considered to be statistically significant by the Sponsor.

As described in published consensus documents (e.g., Borowitz DS, Grand RJ, Durie PR, et al., J Pediatrics, Nov 1995), decreased CFA is an accepted indicator of EPI, and an increase in CFA is associated with enhanced pediatric growth and development. Thus, the change in CFA can be used as a reasonable marker for pancreatic enzyme activity. A clinically meaningful increase in CFA in CF patients is accepted to be an increase of 30% or greater in the most severely affected patients (i.e., those patients who have baseline CFA less than 40%). There is no accepted clinically meaningful increase in CFA that has been determined for patients with EPI due to causes other than CF; however, as EPI due to any cause has similar clinical findings, it would be reasonable to consider this degree of change as meaningful in EPI due to pancreatectomy and

chronic pancreatitis. In addition, there is no accepted change in CFA that has been shown to be clinically meaningful in patients with a Baseline CFA greater than 40%. Patients with higher CFAs at baseline tend to have smaller increases in CFA with PEP administration, as these patients have a lesser capacity to respond. Therefore, and in concert with the Agency's "Guidance for Industry Exocrine Pancreatic Drug Products – Submitting NDAs", the Division accepts the use of CFA as the primary efficacy measure in the pivotal study, 06-001, as reasonable and appropriate.

The Sponsor's results show that the mean CFA for patients receiving Pancrecarb was 83%; the mean CFA for patients receiving placebo (no treatment) was 46%. Therefore, the mean change in CFA was 36%. The efficacy results show a mean change in CFA that was statistically significant ($p < 0.001$; 95% CI [28, 45]). The FDA Statistician confirmed the results and was in agreement with the Sponsor. The results are summarized in Table 27 (electronically copied and reproduced from the Sponsor's submission).

Table 27: Comparison of Percent Coefficient of Fat Absorption (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
Overall (n = 21)	82.458	46.296	36.162[a]	27.781, 44.543
Children (n = 10)	80.841	45.834	35.007[a]	22.888, 47.127
Adults (n = 11)	84.075	46.758	37.317[a]	25.848, 48.786

[a] $P<0.001$

Source: 06-001 Study Report (Page 48, Section 11.1.1, Table 11-1)

The results of the primary endpoint show a statistically significant mean change in CFA in patients treated with Pancrecarb as compared to patients on placebo (no treatment). The clinical significance of a mean change in CFA of 36% is challenging to interpret as this is an average of all of the patients, regardless of their placebo CFA values. Thus, the primary endpoint results should be examined in conjunction with the changes in CFA for individual patients. This was performed as a subgroup analysis by this Reviewer (see section 5.3.1.11.6.2 above).

Overall, the additional efficacy analysis of change in CFA by no-treatment CFA showed that the increase in CFA on Pancrecarb treatment is greatest in the most severely affected patients. For patients (n=9) with a placebo-treatment CFA <40%, the mean increase in CFA on Pancrecarb treatment was 51%, which is a clinically meaningful increase in CFA. The patients who had a higher no-treatment CFA ($\geq$40% during placebo treatment) showed smaller increases in CFA after treatment with Pancrecarb. The inverse relationship between low no-treatment CFA and change in CFA (the lower the value initially, the higher the increase) is critical to the efficacy of the study. These results support the approval of Pancrecarb for the treatment of EPI; treatment with Pancrecarb is beneficial to most patients. The treatment affect is variable; however, it

follows a trend that the greatest change in CFA is observed in the patients with the lowest no-treatment CFA.

For Study 97-001-1B, the following populations are defined for the purposes of the efficacy analysis:

- Intent-to-Treat (ITT) Population: defined as all patients randomized to the study and who completed both treatment phases.

- Per Protocol (PP) Population: defined as all patients that were randomized and completed the study without major protocol deviations. This analysis was performed using the data from the repeat studies for patients 002, 003, and 009 at the Cincinnati site and 004 and 009 at the Indianapolis site and excluding patient 011 at the Indianapolis site.

The ITT results, listed below in Table 28, showed (b) (4)

The Sponsor also used a PP population which showed (b) (4)

Table 28: Efficacy Results Study 97-001-1B

	Pancrecarb MS-8 Mean (SD)	Usual EC Enzyme Mean (SD)	P-value
ITT Population (n=19) CFA (%)	(b) (4)		
PP Population (n=18) CFA (%)			

Source: Adapted from Statistical Reviewer's Table (the results concur with those from the sponsor)

This reviewer performed an analysis of each individual's response to change in treatment (from Pancrecarb to placebo or vice versa).These results are shown below in Table 29, which represents the ITT population and Table 30, which represents the PP population. When analyzing the individual patient results, (b) (4)

Clinically, an individual patient may have improved symptoms of malabsorption (diarrhea, abdominal pain, flatulence) with increasing CFA values.

Table 29: Efficacy Results (CFA) Study 97-001-1B (ITT population)

(b) (4)

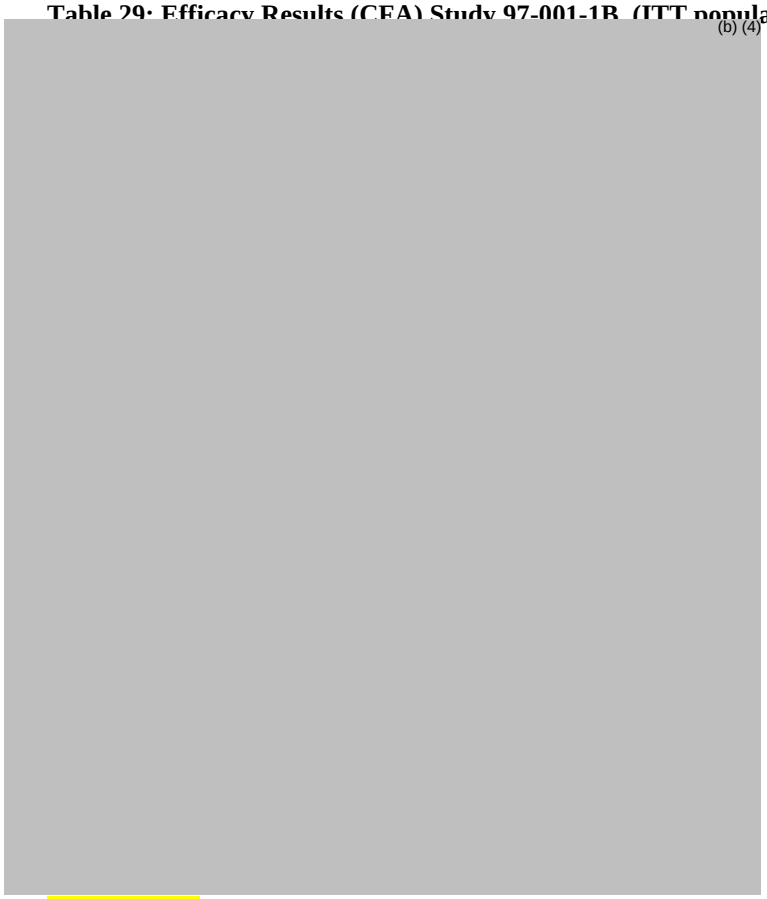

Table 30: Efficacy Results (CFA) Study 97-001-1B (PP population)

(b) (4)

The outcomes for the two populations were vastly different; statistical significance could be shown in the PP population but not the ITT population.

According to the statistical reviewer, this study lacked clinical trial rigidity; it was open-label, there was no washout period between two crossover treatment periods, there were repeated treatment assessments, there was a change of analysis plan, etc. Therefore, the efficacy results were not reliable (b) (4).

In addition, in each individual patient, the changes in CFA were not clinically meaningful. It is difficult to determine the clinical significance of CFA values that differ by (b) (4) (b) (4)

6.1.5 Analysis of Secondary Endpoint(s)

There were several secondary efficacy endpoints Study 06-001. These endpoints evaluated other factors that may help to support the results of the primary efficacy analysis; (b) (4). The secondary efficacy endpoints analyzed had no clinically definable change that was clinically meaningful.

Coefficient of Nitrogen Absorption (CNA)

A major secondary endpoint was the comparison of CNA after administration of Pancrecarb versus placebo.

The results showed that the mean CNA for Pancrecarb and placebo were 79% and 47%, respectively. The mean change in CNA was 32%, and this was a statistically significant change. (See Table 31 electronically scanned and copied from Sponsor.) These results were confirmed by the FDA Statistical Reviewer.

Table 31: Comparison of Percent Coefficient of Nitrogen Absorption (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
Overall (n = 21)	78.986	47.169	31.817[a]	26.102, 37.533
Children (n = 10)	78.440	43.810	34.630[a]	26.365, 42.895
Adults (n = 11)	79.532	50.528	29.005[a]	21.183, 36.826

[a] $P<0.001$

Source: 06-001 Study Report (Page 49, Section 11.1.1.2.1, Table11-3)

These results are supportive of a positive enzymatic effect of PEP treatment; however, a clinically meaningful change in CNA has not been established, so the clinical relevance of these results is not known.

Stool Frequency

A secondary endpoint was the comparison of stool frequency (number of bowel movements) between Pancrecarb and placebo recorded over the 72-hour stool collection period;
The overall results showed stool frequency was 6.1 bowel movements/72 hours for Pancrecarb versus 10.1 for placebo treatment. The difference of 4, a 39.6% decrease in stool frequency with Pancrecarb compared to placebo treatment was statistically significant ($P<0.001$). (See Table 32 electronically scanned and copied from Sponsor)

Table 32: Comparison of Stool Frequency (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
Overall (n = 21)	6.086	10.089	-4.004[a]	-5.607, -2.400
Children (n = 10)	5.591	9.409	-3.817[b]	-6.136, -1.499
Adults (n = 11)	6.580	10.770	-4.190[a]	-6.384, -1.995

[a] $P<0.001$, [b] $P=0.003$

Source: 06-001 Study Report (Page 50, Section 11.1.1.2.2, Table11-5)

Although statistically significant, the clinical significance of a four bowel movement difference over a 72 hour period is not clear.

Stool Weight

Another secondary endpoint was the comparison of stool weight between Pancrecarb and placebo recorded over the 72-hour stool collection period. The overall results showed stool weight was 655.9 g/72 hours for Pancrecarb versus 1308.5 for placebo treatment. The difference of a 652.6 gram decrease in stool weight with Pancrecarb compared to placebo treatment, was statistically significant ($P<0.001$). (See Table 33 electronically scanned and copied from Sponsor)

Table 33: Comparison of Stool Weight (Mixed Model ANOVA, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 minus Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
Overall (n = 21)	655.939	1308.524	-652.585[a]	-813.369, -491.801
Children (n = 10)	507.129	1086.246	-579.117[a]	-811.610, -346.624
Adults (n = 11)	804.748	1530.802	-726.053[a]	-946.082, -506.024

[a] $P<0.001$

Source: 06-001 Study Report (Page 51, Section 11.1.1.2.3, Table11-7)

Once again, the clinical significance of a 653 gram difference in stool weight over a 72 hour period is not clear.

These secondary efficacy variables were difficult to analyze accurately given the multiple variables involved and the nature of the underlying disease. Most secondary endpoints were subjective and assessed without using validated endpoint measures. Study 06-001 was of short duration and had a disproportionate amount of Pancrecarb treatment time, which made the analysis of treatment differences more difficult.

(b) (4)

For study 97-001-1B, the secondary efficacy endpoint was the comparison of CNA after administration of Pancrecarb MS-8versus usual enzyme treatment.

In the ITT population, the results showed (b) (4)

In addition, since the clinical significance of CNA is not established, these secondary efficacy results are not clinically meaningful. (See Table 34 electronically scanned and adapted from Sponsor). These results were confirmed by the FDA Statistical Reviewer.

Table 34: Secondary Efficacy Results

	Pancrecarb MS-8 Mean (SD)	Usual EC Enzyme Mean (SD)	P-value
ITT Population (n=19) CNA (%)	(b) (4)		
PP Population (n=18) CNA (%)			

6.1.6 Other Endpoints

There are no other endpoints evaluated that are of clinical relevance.

6.1.7 Subpopulations

Subgroup analyses by age, and gender were performed by this Reviewer, and were found not to have affected the efficacy results in Study 06-001. There were too few non-Caucasian patients to perform a meaningful analysis by race. Since CF patients are mostly Caucasian, the homogeneity of race in the clinical development plan was felt to be representative of the larger CF population.

Analysis of patients by placebo (no treatment) CFA subgroups showed that the patients who were the most severely affected (lowest baseline CFA) gained the most benefit of Pancrecarb MS-16 treatment by having the largest increase in CFA (see section 6.1.4 Analysis of Primary Endpoint above).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All patients (except one) in the Pancrecarb clinical development program were treated according to CFF guidelines, and dosing did not exceed 2,500 U lipase/kg/meal and 10,000 U lipase/kg/day. The dose of Pancrecarb was determined on an individual basis, and patients' doses were titrated to control their symptoms of EPI while remaining within CFF guidelines.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and/or tolerance effects was not assessed in the Pancrecarb clinical development program since the clinical data obtained were from short-term studies. According to the literature, there does not appear to be the development of tolerance to PEPs and patients remain on these medications for long periods of time (typically life-long treatment).

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Study 97-001-2

This clinical study was a nonrandomized, open label, active controlled one-way cross-over study of ~50% decreased dose of Pancrecarb MS-8 in six CF patients ages 4-17. The primary endpoint was the change in CFA between usual PEP dose of Creon 10 or Creon 20 (Phase 1) and the ~50% reduced lipase dose of Pancrecarb (Phase 2). The results showed (b) (4) The individual efficacy results are displayed below in Table 35.

Table 35: Study 97-001-2 Individual Results

Patient Number	CFA Phase 1 Creon 10	CFA Phase 1 Creon 20	CFA Phase 2 Pancrecarb	Phase 2 - Phase 1
001003	(b) (4)			
001006				
001007				
001011				
001015				
001017				
Mean				

6.1.10.2 Study 2001-180

This clinical study was a nonrandomized, open label, active controlled one-way cross-over study of 50% decreased dose of Pancrecarb MS-4 in six CF patients ages 5-15. Pancrecarb MS-4 was administered to patients via gastrostomy tube (G-tube). The primary endpoint was the change in CFA between usual PEP dose (Phase 1) and 50% decreased dose of Pancrecarb MS-4 (Phase 2) directly into the G-tube. (b) (4)

Table 36: Study 2001-180 Individual Results

Patient Number	Phase	CFA (b) (4)
001001	1	
	2	
001003	1	
	2	
001004	1	
	2	
001005	1	
	2	
001006	1	
	2	
001007	1	
	2	

6.1.10.3 Study 092100

This clinical study was a randomized, double blind, placebo controlled, two-way cross-over study in of Pancrecarb MS-8 in Reducing Diarrhea Associated With Highly Active Antiretroviral Therapy (HAART) in HIV-Positive Patients. The primary efficacy variable was the reduction in frequency of diarrhea. The primary endpoint was comparison of number of formed stools between treatment periods (Pancrecarb MS-8 vs. placebo). (b) (4)

No further analyses were performed on this study.

There were no other relevant efficacy analyses performed.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Safety data were reviewed from the nine clinical studies performed in the Pancrecarb clinical development program, including the two controlled studies 06-001 and 97-001B. Study 06-001 and 97-001B have been described in detail above in Section 5.3. The remaining studies included a number of different study designs (e.g., randomized, active-controlled, placebo-controlled, crossover, blinded, open-label and long-term follow-up). Study 092206 was an open-label placebo-controlled, single-treatment bioavailability study to determine the intestinal bioavailability of Pancrecarb in chronic pancreatitis (CP) patients with EPI. Safety was assessed in these studies by the review of all of the AE data.

The most important study reviewed for safety was 06-001, which was the double blind, placebo-controlled study in CF patients; however, all of the safety data from the Pancrecarb clinical studies were reviewed in its entirety.

7.1.2 Adequacy of Data

In the opinion of this Reviewer, the Sponsor adequately categorized the adverse events using MedDRA classification.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

There was general pooling of safety data for this review. Although, the study designs were different, most of the studies had a similar patient population (CF patients) and many had a similar primary endpoint (change in CFA). In addition, for the two controlled studies, each study was analyzed separately (see Section 5 above).

7.2 Adequacy of Safety Assessments

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

The safety of Pancrecarb was evaluated in nine clinical studies. In eight individual studies, subjects were treated for one to four weeks duration with Pancrecarb. In one study, patients receiving Pancrecarb were followed for up to 2 years. The safety population was defined as any subject who received at least one dose of Pancrecarb. Thus, the safety population includes 262

subjects exposed to Pancrecarb covering a treatment period of seven days to more than two years.

According to the PEP Guidance, it was acceptable that the Pancrecarb clinical program was limited to short-term efficacy and safety studies with the one exception of Study 091897, which was a long-term, non-randomized, uncontrolled, open-label study. The long-term safety of PEPs has been established over the many years of their use. This application relied on the published medical literature for full descriptions of AE profiles.

The overall exposure to Pancrecarb was as follows in Table 37 (electronically copied and reproduced from the Sponsor's submission).

Table 37: Mean Lipase Doses and Duration of Dosing in Clinical Studies

Study No.	Duration of PANCRECARB® Treatment	Lipase Dose Measure	PANCRECARB® Mean Lipase Units		Comparator Mean Lipase Units
06-001			PANCRECARB® MS-16		Placebo
	7 days	Units/kg/meal	1,565 (SD 563)		n/a
97-001-1B			PANCRECARB® MS-8		Usual Enzyme*
	7 days	Units/kg/meal	1,158 (SD 429)		1,145 (SD 448)
		Units/kg/day	4,237 (SD 1,873) [a]		4,189 (SD 1,913)
091897			PANCRECARB® MS-8		Initial History
	Up to 2 years	Units/kg/day	4,576 (SD 3,071)		9,898 (SD 12,004)
97-001-2			PANCRECARB® MS-8		Creon® 10 or 20
	7 days	Units/kg/day	8,682 (SD 3,369)		16,519 (SD 7,207)
071503			PANCRECARB® MS-16		Usual Enzyme*
	14 days	Units/kg/day	5,430 (SE 510)		7,838 (SE 637)
2001-180			PANCRECARB® MS-4		Viokase® powder [b]
	30 days	Units/kg/day	4,490 (SE 1,251)		9,128 (SE 1,251)
020296			PANCRECARB® MS-8 [c]		Cotazym® ECS-8
	14 days	Units/kg/day	6,071 (SD 1,072)		6,810 (SD 1,860)
111395			PANCRECARB® MS-8 [c]		Usual Enzyme**
			Phase 2	Phase 3	Phase 1
	14 days (per phase)	Units/day	273,143 (SD 153,014)	192,503 (SD 87,907)	323,200 (SD 153,823)
		Units/kg/day [d]	5,811	4,096	6,875
092100			PANCRECARB® MS-8		Placebo
	7 days	Capsules/Day	6.9 (SD 2.8)		n/a

*Creon® 20 (Solvay Pharmaceutical); Pancrease® MT-10 and MT-20 (Ortho/McNeil); Ultrase® MT-12, MT-18 and MT-20 (Axcan/Scandipharm)
**Creon® 20 (Solvay Pharmaceutical); Pancrease® MT-16 (Ortho/McNeil); Ultrase® MT-20 (Axcan/Scandipharm); Cotazym® ECS-8 (Organon)
[a] Units/kg/day represent an approximate 48% reduction from the patients' usual lipase dose of 8,760 units, calculated from the average of the range of the number of capsules per day at study entry.
[b] Viokase® is a registered trademark of Axcan/Scandipharm.
[c] A previous formulation low-buffered (1.4mEq) PANCRECARB® (pancrelipase) MS-8 drug product was used in these studies.
[d] Units/kg/day estimated using a mean body weight of 47kg.
n/a = not applicable

The data in the Pancrecarb clinical development program were limited by several factors which included: small study size, use of only one pivotal study, a homogeneous study population, and short study duration. However, given the extensive knowledge of PEPs worldwide, the overall Pancrecarb safety program was adequate for the MS-16 dosage strength, and was consistent with the recommendations of the Guidance.

7.2.2 Explorations for Dose Response

No formal dose-response investigations were performed, but all patients were titrated to relief of symptoms, and remained within CFF guidelines (except one patient). All of the dosage strength tablets were used in the clinical development program; however, only the MS-16 dosage strength had its efficacy demonstrated.

7.2.3 Special Animal and/or In Vitro Testing

Given the extensive human exposure to PEPs, the PEP Guidance for submitting NDAs states that animal pharmacology studies with the active ingredient (pancrelipase) are not needed to support the Pancrecarb clinical development program. In addition, this was a 505(b)(2) application, thus no special animal or in vitro testing was required.

7.2.4 Routine Clinical Testing

The schedule of clinical assessments performed for the pivotal study, 06-001, was adequate (see schedules of study visits for Study 06-001 in Section 5.3), and consisted predominantly of monitoring for AEs during study drug treatment, and changes from baseline in physical examinations (including vital signs) and clinical laboratory assessments (chemistry, hematology and urinalysis). The efforts to elicit AEs were acceptable. Since PEPs are not absorbed, no ECGs were collected.

Clinical laboratory evaluations were conducted in only three studies: 06-001, 111395 and 2001-180. Vital signs and physical examination information were collected while on treatment with Pancrecarb only in Studies 06-001, 111395, and 071503.

7.2.5 Metabolic, Clearance, and Interaction Workup

Pancrecarb acts locally in the GI tract to improve the absorption of lipids, fat soluble vitamins, proteins, and to a lesser extent carbohydrates; it is not systemically absorbed and absorption, distribution, metabolism, and elimination (ADME) assessments were not performed.

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

There is an extensive history of clinical use with the PEPs, and their safety profile is well described. The most serious safety concern with PEP administration is fibrosing colonopathy (FC). FC is a condition that has been reported mainly in young children with CF who are being administered delayed-release PEP formulations. Although the exact etiology of FC is not known, studies have shown that the majority of the patients in whom FC developed were taking high dose PEPs. As a result of this potential safety (and efficacy) concern, the CFF and FDA published weight-based dosing guidelines for PEP administration (see Section 2.1).

The clinical development program for Pancrecarb followed the current CFF recommendations on limiting the dosages (by lipase units). No cases of fibrosing colonopathy were reported in the

clinical development program; however, it is noted that cases of FC are rare, and the finding of even a single case of FC in a safety population of this size was not expected.

PEP treatment has been associated with elevated serum and urine levels of uric acid (hyperuricemia and hyperuricosuria). Uric acid levels were adequately monitored throughout the pivotal clinical study. No clinically significant uric acid elevations were reported; however, given the short duration of treatment and the treatment of patients who were of adequate nutritional status only, most of whom were maintained on stable doses of PEPs prior to entry into these studies, clinically meaningful changes in uric acid levels were not expected.

Despite the negative findings for FC, hyperuricemia, and hyperuricosuria in the short-term clinical development program for Pancrecarb in a small number of patients, given the concerns for these AEs with the administration of PEPs, caution should be exercised when prescribing PEPS to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels. In addition, monitoring for FC should be addressed in any future labeling for Pancrecarb, and should be a component of ongoing safety monitoring/pharmacovigilence of Pancrecarb.

7.3 Major Safety Results

7.3.1 Deaths

Four deaths were recorded during the 2-year long term (091897) study period; none were attributed to the use of Pancrecarb MS-8. No other deaths were reported during any other study with Pancrecarb. The deaths are summarized below in Table 38 (electronically copied and reproduced from the Sponsor's submission).

Table 38: Summary of Deaths Recorded during Study 091897

Subject	Demographics	Cause of Death	Date Enrolled	Date of Death
01A-001	Male, Age 10	Sepsis, neurological insult	8/1998	(b) (6)
12A-04A	Female, Age 44	Evac pseudo pneum/malnutrition, end stage disease	10/21/1998	
17A-009	Male, Age 27	Acute rejection of double lung transplant	8/1/1999	
18A-003	Female, Age 30	Pulmonary disease	1/24/2000	Unknown
Reference: Study 091897 CSR Table 8				

7.3.2 Nonfatal Serious Adverse Events

Overall in the Pancrecarb clinical development program, three Pancrecarb treated patients experienced four AEs that were considered serious by the study investigator(s). None of the SAEs were considered related to treatment. Following are summary narratives of the individual SAEs.

Study 071503: During the Phase 2 (Pancrecarb MS-16) treatment period, one patient (Site 2: #111) was hospitalized with 2 SAEs, "CF exacerbation" and "sinusitis" which were categorized as mild in intensity and not related to study medication. These events were actually first reported as symptoms in Phase 1. The events completely resolved during the study observation period

Study 2001-180: During the Phase 2 (Pancrecarb MS-4) treatment period, one patient (001004) reported being involved in a motor vehicle accident (MVA) and was hospitalized, resulting in their discontinuation from the study. The event was categorized as moderate intensity, definitely not related to study drug, and resolved completely.

Study 06-001: At the follow-up visit (Day 14) at the end of Treatment Period 2, a 10 year old female patient (184-002) experienced an SAE of CF. The patient received Pancrecarb MS-16 during Treatment Period 2. The SAE was assessed as mild and judged not related to the study drug by the Investigator. The SAE was treated with concomitant medication, although no new concomitant medication was prescribed. The SAE was assessed as resolved at an unscheduled visit to follow the SAE.

7.3.3 Dropouts and/or Discontinuations

Overall, 22 patients (8%) from the total safety population of 262 discontinued for reasons attributed to AE(s), 18 of those 22 were receiving Pancrecarb. Table 39 below summarizes the details for individual patients who discontinued due to AE(s). The majority of the AE(s) were gastrointestinal in nature. The long-term study (091897) contributed 13 of the 18 Pancrecarb patients who discontinued due to AE(s). These discontinuations were reported on the CRF AE page and were included in the ISS AE database. The Sponsor reports that an additional seven patients discontinued Study 091897 for reasons noted to be due to AE(s) on the CRF clinical summary page. However, due to insufficient information, these events were not included in the ISS AE database.

This reviewer examined the reports for each of the additional seven patients who were discontinued from the study 091897 due to an adverse event. Every discontinuation was secondary to an AE which was gastrointestinal in nature.

Table 39: Discontinuations Attributed to AEs

Study Number	Treatment Group	Patient number	Adverse Event	Intensity
06-001	Placebo	007-006	Decreased weight	Moderate
06-001	Placebo	009-005	Hyperglycemia and elevated LFTs	Moderate Moderate
111395	Usual lipase	005	Stomach ache	Moderate
97-001	Usual lipase	001006	Pulmonary exacerbation and Fever	Severe Severe
071503	Pancrecarb	001	Nausea and Abdominal cramps	Moderate Moderate
97-001-2	Pancrecarb	001007	Fever	Severe
111395	Pancrecarb	008	Abdominal pain	Moderate
111395	Pancrecarb	009	Stomach cramping	Moderate
020296	Pancrecarb	017	Abdominal discomfort	Moderate
091897	Pancrecarb	10A110	Blood in stool	Mild
091897	Pancrecarb	10A111	Abdominal pain and Malabsorption	Severe Moderate
091897	Pancrecarb	10A112	Cramps and malabsorption	Severe Severe
091897	Pancrecarb	12A001	Abdominal cramp and diarrhea	Severe Severe
091897	Pancrecarb	12A010	Abdominal cramps and diarrhea	Severe Severe
091897	Pancrecarb	13A003	Increased bloating and gas	Moderate Moderate
091897	Pancrecarb	13A006	Increased number of stools and gas	Moderate Moderate
091897	Pancrecarb	13A008	Fat in stools and increased of stools	Moderate Moderate
091897	Pancrecarb	13A011	Increased BM's, gas, pain	Unknown
091897	Pancrecarb	13A020	Increased number of stools	Moderate
091897	Pancrecarb	13A024	Increased abdominal pain and gas	Moderate Moderate
091897	Pancrecarb	13A026	Increased bloating gas and pain	Unknown
091897	Pancrecarb	16A009	Increased gas	Moderate

7.3.4 Significant Adverse Events

The long term study (091897) was comprised of CF patients that were on Pancrecarb MS-8 therapy for up to 2 years. In this study, hospitalization alone was not considered a SAE. Based on the study design and documentation instructions, if hospitalization was related to Pancrecarb the "Adverse Experience Report" form was to be completed. Overall, 45 subjects enrolled in the long term study (091897) were hospitalized at some time during the 2-year study period. Hospitalizations were mostly due to CF disease related events. None of the hospitalizations were considered by the study site investigators or this Reviewer to be related to the use of pancreatic enzymes.

During Study 111395, two patients (004 and 007) were hospitalized due to exacerbation of their underlying CF. These hospitalizations were not reported as SAEs per the protocol. Both patients completed the study and the events were not considered related to enzyme treatment.

Two cases of hypersensitivity reactions were reported:

- In Study 97-001B, a 17-year-old male (patient #005), experienced a moderate intensity rash during Phase 2 (Pancrecarb MS-8) which was considered possibly related to study medication. No action was taken and the event resolved completely.
- In Study 06-001, a 17-year-old female (patient 007-009), experienced a mild rash during Phase 2 (Pancrecarb MS-16) which was considered unrelated to study medication, and which resolved with concomitant medication.

7.3.5 Submission Specific Primary Safety Concerns

The most serious safety concern with PEP administration is fibrosing colonopathy (submucosal fibrosis). See section 7.2.6 (above).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Since the Pancrecarb development program consisted of nine clinical studies, many of which had different study designs, AEs in patients treated with Pancrecarb were analyzed separately from those AEs in patients taking their usual PEP (active control) and patients taking placebo. The assessment of AEs for causality and severity were made by the clinical investigator(s) responsible for each respective study.

Pancrecarb
Of the 262 patients treated with Pancrecarb that were enrolled in a total of 9 clinical studies, 77 (29%) experienced 148 adverse events. Of these, 36 (14%) patients experienced at least one AE that was possibly, probably or definitely related to treatment The most commonly reported AE (>5% incidence) in the Pancrecarb treated safety group was abdominal pain, with 14 events reported, 11 of which were considered related to treatment. There were 7 reports of severe abdominal pain, 6 of which were considered related to treatment. Other AEs reported for patients treated with Pancrecarb included abdominal pain upper and headache (n=8 each), diarrhea and flatulence (n=7 each), abdominal distension and frequent bowel movements (n=6 each). Three patients experienced four AEs that were considered serious by the study investigator(s). None of the SAEs were considered related to Pancrecarb treatment [see Section 7.3.2.].

Usual Lipase
There were six active-controlled studies included in the Pancrecarb NDA. The following brands of PEPs were included in these studies: Creon® 10 and 20 (Solvay Pharmaceutical); Pancrease® MT-10, MT-16 and MT-20 (Ortho/McNeil); Ultrase® MT-12, MT-18 and MT-20 (Axcan/Scandipharm); Cotazym® ECS-8 (Organon), and Viokase® powder (Axcan/Scandipharm).

Of the 87 patients treated with their usual lipase, 20 (23%) experienced 26 adverse events. Of these, 7 (8%) patients experienced at least one AE that was possibly, probably or definitely related to treatment. There were no SAEs reported.
The most commonly reported AE (>2% incidence) in the usual lipase treatment group was headache, with six events reported which were considered related to treatment. There were two reports of moderate abdominal pain which were considered related to treatment. There were two reports of severe pyrexia which were not considered related to treatment.

Placebo
There were two placebo-controlled studies included in the Pancrecarb NDA. Of the 37 placebo treated patients, 18 (49%) experienced 65 adverse events. Of these, 15 (40%) patients experienced at least one AE that was possibly, probably or definitely related to treatment. There were no SAEs. The most commonly reported AEs (>5% incidence) in the placebo treatment group were abdominal pain/distension, flatulence, headache, and decreased weight, the majority of which were considered related to treatment. There were two reports each of nasal congestion and pharyngolaryngeal pain which were not considered related to treatment.

For a detailed review of adverse events for Study 06-001 and Study 97-001-1B see Sections 5.3.1.11.7.2 and 5.3.2.11.3.2.

7.4.2 Laboratory Findings

Clinical laboratory evaluations were conducted in only three studies: 06-001, 111395 and 2001-180. In Study 06-001, there were two patients who had laboratory results that were considered by the investigator to be clinically significant. One patient (009-005) had hyperglycemia and elevated liver function tests while on placebo during Treatment Period 1. One patient (007-008) on Pancrecarb had an abnormal urinalysis (which showed large hemoglobin) at the end of Treatment Period 2. However, both these abnormalities were present at Screening and slightly improved at the End of Study Visit and Follow-up visits.
This review identified an additional patient (191-003) in Study 06-001 who had an elevated alkaline phosphatase level after Treatment Period 1 (580 U/L) and a markedly elevated alkaline phosphatase level at the Follow-up visit (1445). Of note, is that this patient had a history of "active CF liver disease" and baseline elevated blood levels of AST, ALT and GGT.

This reviewer reviewed these individual cases and concluded that these isolated cases could not confer clinical meaningfulness. No clinical consequences were noted from any of the above findings.

Study 111395 was a ten patient non-randomized, open-label, active-controlled, one-way crossover study wherein an older formulation (b) (4) of Pancrecarb was used. Clinical laboratory testing was performed at baseline and after completion of each of the two Pancrecarb dosing phases. This reviewer reviewed the laboratory values for each patient; there were no clinically relevant changes in laboratory values.

Study 2001-180 was a seven patient non-randomized, open-label, active-controlled, one-way crossover study wherein the MS-4 dosage formulation was administered into a gastrostomy tube. This reviewer reviewed the laboratory values for each patient; there were no clinically relevant changes in laboratory values.

7.4.3 Vital Signs

Vital signs and physical examination information were collected while on treatment with Pancrecarb only in studies 06-001, 111395, and 071503. In these studies, no clinically relevant changes were observed.

7.4.4 Electrocardiograms (ECGs)

Pancrecarb is not systemically absorbed and electrocardiogram evaluation was not part of the Pancrecarb clinical development program.

7.4.5 Special Safety Studies

There were no special safety studies performed in the Pancrecarb clinical development program.

7.4.6 Immunogenicity

Pancrecarb and other porcine-derived PEPs are not systemically absorbed, and immunogenicity testing was not performed as part of the Pancrecarb clinical development program.

7.5 Other Safety Explorations

No other safety explorations were performed. No non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Pancrecarb and other porcine-derived PEPs are not systemically absorbed and human carcinogenicity studies were not part of the PEP clinical development program.

7.6.2 Human Reproduction and Pregnancy Data

No studies with Pancrecarb were conducted in pregnant women. It is likely that Pancrecarb will be used by pregnant women and women of reproductive potential. PEPs have likely been used over their history by pregnant women, but are not absorbed and no known effects of active

ingredients on pregnant women or their offspring are known. The labeling of this product should address safety in pregnancy.

7.6.3 Pediatrics and Effect on Growth

PEPs are widely recognized as having a positive effect on growth in pediatric patients with CF.[4,5] Studies performed in the Pancrecarb clinical development program were, for the most part, short-term studies where long-term growth and development were not assessed, which is consistent with the recommendations for study designs in the Guidance for submitting PEP NDAs. One long -term (up to two years) study, 091897, which was performed as part of the Pancrecarb clinical development program, had weight gain as the primary endpoint. However, the non-randomized, uncontrolled, open-label study design did not allow for reliable interpretation of the data. Thus, no accurate formal assessments of pediatric growth and development were performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

PEPs are not systemically absorbed and there is no potential for abuse, withdrawal, or rebound.

An important safety issue regarding PEP use and the potential for overdose is fibrosing colonopathy (FC). The etiology of FC has not been definitively established, but is thought to be associated with high dose lipase exposure, although some reports indicate the risk of FC is associated with the excipients.[4, 5] In order to optimize therapy while minimizing the risk of FC, the Cystic Fibrosis Foundation (CFF) in conjunction with the FDA recommends starting lipase doses according to age as described below.

The CFF recommends the following dose schedule for full meals:

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.
- Children <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.

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[4] Borowitz, DS; Grand, RJ; Durie, PR; Consensus Committee (sup A). Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. J Pediatrics.127(5), Nov 1995, pp 681-684. (PMID: 7472816)

[5] Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol. 2006; 20(3):531-46. (PMID: 16782527)

- 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.

Recommendations for snacks are half the dose taken at meals. Daily doses are not to exceed 10,000 U lipase/kg/day (3 meals, 2 snacks).

These recommendations should be included in product labeling for Pancrecarb and for all PEPs.

7.7 Additional Submissions

A 120-Day Safety Update Report was submitted by the Sponsor on March 17, 2009. Pertinent findings from the report are presented below:

The Sponsor reports that all Pancrecarb studies were completed with the safety information included in the original NDA, with the exception of Study Protocol 092206 entitled *Bioavailability of Pancreatic Enzymes in the Human Upper Intestine (duodenum) from Pancrecarb Delayed Release Capsules, Buffered and Enteric- Coated Microspheres*. Three additional patients have been enrolled at St. Louis University and completed the study with no adverse events reported. Four additional patients have been enrolled at another study site, University of North Carolina: Two patients discontinued the study during Phase 1 (placebo) due to procedurally related emesis, and two patients completed the study with no AEs reported.

Thus, there were no new or additional safety findings reported in the 120-day Safety Update.

8 Postmarketing Experience

Pancrecarb capsules were introduced onto the US market by Digestive Care, Inc. in 1995 as a physician prescribed pancreatic enzyme replacement therapy. Annual Drug Product Reviews have been prepared since 2002. Over this period of time, only two product complaints relating to an adverse drug reaction have been reported. A case of Distal Intestinal Obstructive Syndrome (DIOS) was reported that was determined to be congenital and not considered by the physician to be related to treatment with Pancrecarb, and one case of allergic reaction (itching and red, blotchy rash on face) in a patient with a history of allergy to another pancrelipase product.

The manufacturer does not have specific data on the number of patients treated with Pancrecarb. However, based on distribution data for the annual period of January 2007 through December 2007, approximately (b) (4) Pancrecarb capsules were shipped to wholesalers. If the usual range of daily intake of Pancrecarb is 10 to 20 capsules, this would represent approximately (b) (4) patients currently being treated with Pancrecarb on an annual basis.

9 Appendices

9.1 Literature Review/References

Please see individual references noted throughout this review.

9.2 Labeling Recommendations

Since this NDA is recommended to receive a Complete Response action, the labeling was not negotiated with the Sponsor during this review cycle. However, should Pancrecarb be approved during a future review cycle recommendations for future labeling should include:

- Recommended indication: Pancrecarb is indicated for the treatment of steatorrhea due to EPI due to a variety of causes, including CF and CP.

- Viral issues: Since PEPs are derived from pig pancreata, there is a theoretical and potential risk of transferring certain species-specific viruses to patients taking PEPs (e.g., porcine parvovirus). Thus, labeling should note that live virus are present in the capsule, and that potential risk of transmission exists, although no human transmission due to PEP exposure has been reported to date.

- Dosage recommendations: To follow CFF recommendations; see Section 7.6.4 .

- Warnings: Cases of fibrosing colonopathy has been reported in young CF patients on high doses of PEPs. There have been reports of elevated serum and urine uric acid levels in patients taking PEPs.

- Dosing instructions: do not open microtabs to estimate doses.

- Secondary endpoints: not to be included in labeling.

9.3 Advisory Committee Meeting

No Advisory Committee was convened for this application.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22175	ORIG 1	DIGESTIVE CARE INC	PANCRECARB

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/s/

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