CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-175Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-175 / 000
Drug Name:	Pancrelipase Capsules, Buffered and Enteric-Coated Microspheres, (b) (4), MS-8 and MS-16
Indication(s):	Treatment of Exocrine Pancreatic Insufficiency (EPI)
Applicant:	Digestive Care, Inc.
Date(s):	Stamp Date: 10/27/2008 PDUFA Date: 8/27/2009
Review Priority:	Standard
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Keywords: Clinical studies, NDA review, Crossover design, Repeated measure ANOVA

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The pivotal Study 06-001 showed that PANCRECARB® was effective in increasing coefficient of fat absorption (CFA) level compared to placebo. However, the capsule used in this study was exclusively MS-16 (b) (4)
Based on the clinical data submitted, only the efficacy of PANCRECARB MS-16 can be concluded.

Study 97-001-1B was submitted to support the indication using the MS-8 capsules. 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.

1.2 Brief Overview of Clinical Studies

The ten studies submitted with this NDA 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 was a randomized, double-blind, placebo-controlled, multi-center crossover study. The primary objective of this study was to demonstrate the efficacy and safety of PANCRECARB® MS-16 for reduction of steatorrhea (as measured by 72-hour stool fat determinations) in children and adults with Cystic Fibrosis (CF) and pancreatic insufficiency. A secondary objective was to demonstrate the efficacy of MS-16 in reducing fecal nitrogen loss (as measured by 72-hour stool nitrogen determinations). Additional secondary endpoints were stool frequency and stool weight. The study consisted of a screening period, dose stabilization period, treatment period 1, washout re-stabilization period and treatment period 2. A total of 29 subjects were enrolled (14 children aged no less than 7 to 17 years and 15 adults aged no less than 18 years) were enrolled at five centers in the US. Twenty-four patients (11 children and 13 adults) were randomized and 21 (10 children and 11 adults) completed the study. Analysis of the study results were performed on the overall populations as well as separately for children and adults.

Study 97-001-1B was a randomized, open-label, active-controlled, two-way crossover study. The objective of this study was to determine the safety and efficacy of MS-8 at approximately 50% reduced lipase dose in reducing fecal fat and nitrogen losses in patients with CF when compared with other enteric-coated (EC) enzyme supplements (patient's usual pancrelipase product). The study was carried out during two consecutive seven-day treatment periods in patients with CF admitted to clinical research center. The dosage of 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 approximately 50% of each patient's routine lipase dose requirement, but not lower than approximately 1,800 USP Units of lipase per gram of fat intake per day. Only those patients with a CFA no more than 85% during the initial approximately 50% reduced enzyme dose were randomly assigned in the two crossover treatment period. Twenty patients at

two study sites were enrolled and randomized to treatment. One patient did not participate in the second arm treatment and was excluded from the efficacy analysis. Nineteen patients completed all study visits.

1.3 Statistical Issues and Findings

The pivotal Study 06-001 was a crossover study and so each patient received both treatments (MS-16 and placebo). The sponsor treated the two treatment outcomes as independent for the treatment effect comparisons; however, for such a crossover design the correlation between the outcomes from two treatments may not be ignorable. Hence, this reviewer performed a t-test of the outcome differences paired up by each patient, and the efficacy conclusion was not altered. Results from both approaches are presented in this statistical review.

It is observed that the treatment effect has a linear relationship with the baseline/placebo condition. In particular, for the primary endpoint, the change in CFA (under MS-16 minus under placebo) decreases as placebo CFA increases. In fact, the treatment effect for subjects with placebo CFA values under 40% is more than twice the effect for those over 40%. It may be interesting to note that there was no patient had placebo CFA values exceed 80% in this study.

Additional analyses including subgroup studies by sequence and period are also performed and presented in this statistical review. No impact from these two factors can be observed.

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.

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; thus the results were not sufficient to support an efficacy claim.

2. INTRODUCTION

2.1 Overview

The pancreas exhibits a variety of exocrine and endocrine functions required for proper digestion, nutrition and metabolism. One of the major exocrine pancreatic functions is the secretion of enzymes in a bicarbonate-rich digestive fluid into the small intestine to digest fats, proteins and starches. Exocrine Pancreatic Insufficiency (EPI) does not occur until the pancreatic enzyme output level is reduced by more than 90%. EPI clinically manifests as

abdominal bloating, cramping, diarrhea and weight loss and is a characteristic of cystic fibrosis (CF) and chronic pancreatitis (CP).

CF, a genetic disorder that primarily affects the respiratory and gastrointestinal systems, is the second most common life-shortening, childhood-onset inherited disorder in the US. Approximately 30,000 people in the US have CF and 90% of all individuals with CF have EPI and are treated with pancreatic enzyme replacement therapy (PERT). The majority of individuals with CF are diagnosed before the age of one year and the diagnosis in this age group is often made due to signs and symptoms associated with EPI.

CP is a result of progressive functional damage to the pancreas and is characterized by the loss of both endocrine and exocrine function. Approximately 80-90% of CP cases reveal a history of excessive alcohol intake. EPI manifests late in the course of CP.

PERT with products containing lipase (to break down fat), protease (to break down proteins), and amylase (to break down complex carbohydrates) has long been accepted as an effective means of reducing the malabsorption of nutrients associated with EPI. The enzymes in older non-EC (enteric-coated) and powdered Pancreatic Enzyme Product (PEP) formulations were largely inactivated by gastric acidity, with less than 10% of the lipolytic and 20% of the tryptic activity reaching the ligament of Treitz in the duodenum. The introduction of pH-controlled EC enzyme preparations has improved the effectiveness of PEPs.

However, the enzymatic activity of EC PEPs is variable, especially for lipase content. The potential reasons include: 1) the enzymes could be partially inactivated by gastric conditions; 2) the enzymes lack a favorable basic microenvironment for optimized lipase activity; and 3) the EC particles are physically too large. Administration of exogenous pancreatic enzyme extracts as a treatment for EPI in an attempt to normalize digestion is usually only partially successful and some patients continue to suffer from maldigestion.

PANCRECARB® is a bicarbonate-buffered and EC pancrelipase formulation. The sponsor claims that the bicarbonate in the PANCRECARB® formulation establishes a suitable microenvironment surrounding the microspheres in the pH range of 8.5 to 9.0 that theoretically provides optimal lipase activity for digestion of fats and lipids compared to non-buffered formulations. The PANCRECARB® drug product is a solid oral dosage form consisting of clear gelatin capsules containing small EC microspheres.

This NDA includes clinical data for (b)(4) MS-8, and MS-16. The clinical bioavailability, efficacy and safety of PANCRECARB have been evaluated in a total of 10 prospective studies. These include over 270 subjects between the ages of 2 to 79 years, the majority of which are CF patients. This statistical review only focuses on the two controlled Studies 06-001 and 97-001-1B, which support the MS-16 and MS-8 dosages, respectively.

2.2 Data Sources

Materials reviewed include clinical study reports and protocols for Studies 06-001 and 97-001-1B, and Statistical Analysis Plan (SAP) for the pivotal Study 06-001. This application is submitted with data sets for all studies to the Electronic Document Room (EDR) at \\Fdswa150\nonectd\N22175.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study 06-001

3.1.1.1 Study Design and Endpoints

The pivotal Study 06-001 was a randomized, double-blind, placebo-controlled, multi-center, crossover study. The primary objective of this study was to demonstrate the efficacy and safety of PANCRECARB® MS-16 for reduction of steatorrhea (as measured by 72-hour stool fat determinations) in children and adults with CF and EPI. A secondary objective was to demonstrate the efficacy of PANCRECARB® MS-16 in reducing fecal nitrogen loss (as measured by 72-hour stool nitrogen determinations). Additional secondary endpoints were stool frequency and stool weight. The study was conducted in patients, aged 8-43 years, with CF confirmed by positive sweat chloride and/or genotype, and clinical features characteristic of the phenotype. Spot fecal elastase (≤100 µg/g stool) was used to confirm pancreatic insufficiency.

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

Following the Screening Visit that determined eligibility, patients underwent a 7 to 10 days of Dose Stabilization Period with open-label PANCRECARB® MS-16 at home. During that time period, a high-fat diet (approximately 2 gm fat/kg/day) was consumed. Each patient's dose was managed in order to achieve control of pancreatic insufficiency symptoms and to achieve stabilized status according to the clinician's observations and that patient's signs and symptoms. The chosen dose was used during the subsequent treatment periods.

At the beginning of the Treatment Period 1 (6 to 8 days), subjects were randomized either to active study drug or matching placebo. Treatment then occurred with each meal for the next five days. During the Washout/Re-Stabilization Period (7 to 10 days), subjects were treated with open-label PANCRECARB® MS-16, at the same dose as determined during the Dose Stabilization Period, and continued on the high-fat diet at home. During Treatment Period 2 (6

to 8 days), subjects crossed over to either active study drug or matching placebo and repeated the procedure in Treatment Period 1.

On Day 0 of the Treatment Periods, the patient received the supply of double-blinded study drug. The same previously described high-fat diet continued. The subject started the Treatment Period on the morning of Day 1, and Days 1 and 2 were completed at home. On the morning of Day 3, the subject was admitted to the GCRC. Active study drug or placebo was administered with breakfast along with a stool dye marker FD&C Blue #2. On Day 6 (fourth day in the GCRC), a second dye marker was taken with breakfast. If a subject did not pass the first dye marker before the second dye marker was to be administered, the administration of the second dye marker would be delayed by 24 hours. If the subject did not have a bowel movement within 36 hours of the dye administration, or at anytime during the study the subject felt very constipated, the investigator was to prescribe the in-hospital use of laxative. Treatment with study drug and high-fat diet were continued until the next major meal (lunch), at which time the subject resumed his/her previously established dose of PANCRECARB® MS-16. All stool that passed after the appearance of the first dye marker in the stool, up to and including the one with the appearance of the second dye marker, was saved. This constituted the 72-hour stool collection that was used to determine the amount of fat and nitrogen in the stool, which ultimately determine the primary and secondary efficacy endpoint (CFA and CNA [Coefficient of Nitrogen Absorption]) assessments. The subject was discharged to home at the completion of the stool collection.

Upon verification of eligibility, the subject was assigned a unique study subject number. (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 identifiers were prepared for the two age groups, 7 to 17 years, inclusive (Children), and 18 years and older, inclusive (Adults). As the subjects enrolled into the study, the Clinical Project Manager would assign 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.

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 $N = (Z_\alpha + Z_\beta)^2 \times (41.2)^2 \big/ (30\%)^2$, 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…"

3.1.1.2 Patient Disposition, Demographic and Baseline Characteristics

Five US sites enrolled a total of 29 patients with 14 children and 15 adults. Of these 29 subjects, five discontinued prior to randomization (screen failures) and 24 subjects (11 children, 13 adults) were randomized. Three subjects discontinued the study (two due to adverse events [AEs] and

one protocol violation) and 21 subjects (10 children, 11 adults) completed the study. The first enrollment occurred on February 13, 2007, while the last contact occurred on September 4, 2007. A summary of subject disposition by age group is presented in Table 3.1.1 below.

Table 3.1.1. Summary of Subject Disposition

	Children	Adults	Overall
Number of Subjects Enrolled, n (%)	14 (100%)	15 (100%)	29 (100%)
Number of Subjects Discontinuing Study Prior to Randomization (Screen Failure), n (%)	3 (21.4%)	2 (13.3%)	5 (17.2%)
Number of Subjects Randomized, n (%)	11 (78.6%)	13 (86.7%)	24 (82.8%)
Number of Subjects who Received at Least one Dose of Study Drug, n (%)	11 (78.6%)	13 (86.7%)	24 (82.8%)
Number of Subjects Completing Study, n (%)	10 (71.4%)	11 (73.3%)	21 (72.4%)
Number of Subjects Discontinuing Study After Randomization, n (%)	1 (7.1%)	2 (13.3%)	3 (10.3%)
Adverse Event (AE)	1 (7.1%)	1 (6.7%)	2 (6.9%)
Protocol Violation	0 (0.0%)	1 (6.7%)	1 (3.4%)

Source: Study 06-001 Clinical Study Report (Table 14.1.1)

Subjects 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 FDA's IR letter dated April 9, 2009, the sponsor identified three patients that were to be replaced. Two of them were both replaced after their discontinuation during the Treatment Period 1 (one due to an AE and the other protocol violation). The other one discontinued after the Treatment Period 1 due to an AE, but was not replaced since there were already 11 patients in that age group (Children) at the time. The sponsor also clarified that the replacement procedure was simply to register a new patient (once the need was identified) with a new subject number and a new kit.

Populations used for analysis were safety population, completed-treatment population, and per-protocol population. The safety population consisted of 24 subjects who were randomized and received at least one dose of study drug. The safety analyses were conducted on this data set. The completed-treatment population consisted of 21 subjects who were randomized and completed both treatment periods with adequate 72-hour stool collections for analysis. The per-protocol population consisted of 19 subjects who were randomized and completed both treatment periods with adequate 72-hour stool collections for analysis and no major dosing protocol violations. The efficacy analyses were conducted on both of these data sets. There was no missing data handling method proposed due to the definition of the populations used.

Demographic variables are summarized in Table 3.1.2 below. The mean age in children group was 11.8 years and in adults group 26.5 years. More males than females were enrolled in both age groups. The sponsor also reported that medical history, past surgical procedures, and concomitant medications, therapies, and non-drug treatments were all consistent with general CF patients.

Table 3.1.2. Summary of Baseline Demographics (Safety Population)

	Children (n = 11)	Adults (n = 13)	Overall (n = 24)
Age (years)			
Mean (SD)	11.8 (2.96)	26.5 (7.40)	19.8 (9.41)
Min – Max	8 – 17	18 – 43	8 – 43
Gender, n (%)			
Male	8 (72.7%)	10 (76.9%)	18 (75.0%)
Female	3 (27.3%)	3 (23.1%)	6 (25.0%)
Race, n (%)			
White	11 (100.0%)	11 (84.6%)	22 (91.7%)
Black	0 (0.0%)	2 (15.4%)	2 (8.3%)
Height (cm)			
Mean (SD)	144.90 (12.875)	166.37 (7.288)	156.53 (14.805)
Min – Max	126.0 – 164.5	155.0 – 178.0	126.0 – 178.0
Weight (kg)			
Mean (SD)	40.21 (11.765)	58.76 (7.596)	50.26 (13.396)
Min – Max	27.5 – 60.5	45.0 – 66.8	27.5 – 66.8

Source: Study 06-001 Clinical Study Report (Table 14.1.2)

3.1.1.3 Statistical Methodologies

The primary efficacy endpoint was the change in CFA calculated from the 72-hour stool collection and dietary records. The CFA observed during treatment with active study drug (PANCRECARB® MS-16) was compared with the CFA observed during treatment with placebo. CFA was defined as [(total fat intake (g/day) – total fat excretion (g/day)) / total fat intake (g/day)] x 100%. The primary analysis of CFA comparison was performed using a mixed-model analysis of variance (ANOVA) with fixed effects for age group, treatment sequence, treatment group, period, age*sequence interaction, age*treatment interaction, and a random effect for subject within age*sequence.

The secondary efficacy endpoints were:

- The change in CNA calculated from the 72-hour stool collections and dietary records. The CNA observed during the treatment with the active study drug (PANCRECARB® MS-16) was compared with the CNA observed during the treatment with placebo. CNA was defined as [(total nitrogen intake (g/day) – total nitrogen excretion (g/day)) / total nitrogen intake (g/day)] x100%;
- The change in stool frequency (number of bowel movements) between active study drug (PANCRECARB® MS-16) and placebo, recorded over the 72-hour stool collection period;
- The change in stool weight (g) between active study drug (PANCRECARB® MS-16) and placebo, recorded over the 72-hour stool collection period.

These continuous secondary efficacy variables were analyzed using the same model as described above for the primary efficacy variable. There was no multiplicity adjustment strategy proposed.

The statistical methods section in the protocol described that related incidence rates of AEs were compared using Fisher's exact test. The SAP included only descriptive data summaries for related incidence rates of AEs.

The following changes were made to the planned analyses after database lock and unblinding:

- Stool weight was added as a secondary efficacy endpoint;
- A per-protocol population was added to the analysis sets;
- Primary and secondary endpoint efficacy analyses were performed on the per-protocol population.

Therefore, the results for stool weight and per-protocol population should be deemed exploratory (b) (4)

The database was constructed in the data management system (b) (4), and initially locked on October 10, 2007 and final lock on February 28, 2008. After the study was completed, an audit was conducted, and on the basis of audit findings, data queries were issued to the sites. The sponsor claimed that because of the change in data management system (b) (4) during this time, the original database could no longer be opened and updated with the changes resulting from the queries. Therefore, the sponsor decided to update the SAS data set with the revised data. This data set, created on April 15, 2008, was used to generate the tables and listings used to complete the clinical study report. In response to the Agency's IR letter dated April 9, 2009, the sponsor provided the details of all the changes and audit queries. Although the audit only pointed out some mistakes in meal and dosing times, the sponsor made some other changes, including stool records that affected the CFA and CNA values for three patients in the Michigan site. Although the changes were not large and the efficacy analyses results were similar, this review presents the results from both the original (Tables 3.1.3 and A.2) and revised data sets (Table A.3).

3.1.1.4 Results and Conclusions

The comparison of interest was the difference in means between PANCRECARB® MS-16 and placebo. Although the study was not powered to demonstrate treatment benefit within age group, these comparisons were performed secondarily. The least square means and the estimates of the treatment effect, associated *p*-values and 95% confidence intervals (CIs) are presented in Table 3.1.3 below. The results show highly significant treatment effect of PANCRECARB® MS-16 on CFA compared with placebo with over 35% difference, overall and for both age groups. Moreover, the ANOVA model shows no significant impact of the age group, treatment sequence, or treatment period on the results.

Table 3.1.3. Comparison of CFA (%, Completed-Treatment Population)

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 - 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: Reviewer's Table (the results concur with those from the sponsor)

Instead of the model proposed by the sponsor, a simple t-test for two independent samples or a paired t-test shows similar results. Table 3.1.4 below presents the results from the t-tests. It appears that both t-tests rendered consistent results with those from the ANOVA model and the significance difference between two treatment effects can still be concluded.

Table 3.1.4. T-test on Comparison of CFA (%, Completed-Treatment Population)

Age Group	Means		Mean Difference	95% CI of Difference	
	PANCRECARB® MS-16	Placebo	(PANCRECARB® MS-16 - Placebo)	Two independent sample t-test	Paired t-test
Overall (n = 21)	82.614	45.995	36.619[a]	(26.683, 46.555)	(28.697, 44.541)
Children (n = 10)	80.750	45.180	35.570[a]	(19.298, 51.842)	(22.707, 48.433)
Adults (n = 11)	84.309	46.736	37.573[a]	(23.977, 51.168)	(25.692, 49.454)

[a] $P < 0.001$

Source: Reviewer's Table

To further investigate whether or not the sequence and treatment period had any impact on the outcomes, t-test comparisons of CFA between two treatments within treatment sequences and treatment periods are summarized in the Appendix (Table A.1). As indicated in the ANOVA model, the results show no major impact of these two factors.

It is interesting to note that the patient population in this study had generally low CFA under placebo, which usually corresponds to a higher response to the treatment. Table 3.1.5 below shows the summary statistics of CFA under placebo. There was no patient who had placebo CFA higher than 80% and a majority of the patients had placebo CFA below 50% for both age groups.

Table 3.1.5. Summary of CFA (%) under Placebo (Completed-Treatment Population)

	Children (n = 10)	Adults (n = 11)	Overall (n = 21)
Mean (SD)	45.2 (19.68)	46.7 (19.88)	46.0 (19.30)
Min – Max	19.0 – 74.0	18.6 – 77.5	18.6 – 77.5
1st Quartile	29.88	31.80	29.50
Median	43.85	48.10	48.10
3rd Quartile	58.90	60.45	59.20

Source: Reviewer's Table

For the first secondary efficacy endpoint of CNA, significance of the treatment effect can be shown as well (the ANOVA results are presented in Table A.2 in the Appendix). T-tests and within sequence or within period analyses render consistent results. For the other two secondary efficacy endpoints, stool frequency and weight, the results show significant difference between two treatments; however, the results on these two endpoints are not presented in this review due to their lack of clinical importance. The primary efficacy analyses were repeated using the original data before the aforementioned audit and the results are very close to those using the final data. All those results are presented as well in the Appendix (Table A.3).

The sponsor repeated all efficacy analyses on the per-protocol population, which included 19 patients. The results were very similar to those on the completed-treatment population. As

mentioned before, since this per-protocol population was identified after database lock and unblinding, the results on this population should be considered exploratory and are not presented in this statistical review.

The sponsor did not propose any missing data handling method. There were three patients that discontinued during the study; however, none of them had any stool samples. Therefore, it was difficult to justify a meaningful imputation technique. The sponsor identified that two out of these three patients were replaced, and excluding the two replacement patients or imputing their PANCRECARB® results with the placebo results (no treatment effect) did not alter the final efficacy conclusion. Although replacing patients during the course of a study is not deemed good clinical trial practice, it does not seem to have any impact on the efficacy conclusions.

3.1.2 Study 97-001-1B

3.1.2.1 Study Design and Endpoints

The supportive Study 97-001-1B was a randomized, open-label, active-controlled, two-way crossover study. The objective of this study was to determine the safety and efficacy of PANCRECARB® MS-8 at approximately 50% reduced lipase dose in reducing fecal fat and nitrogen losses in patients with CF when compared with other EC enzyme supplements.

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 adjusted to approximately 50% of each patient's routine lipase dose requirement, but not lower than approximately 1,800 USP Units of lipase per gram of fat intake per day.

At the time of the screening visit, all patients had 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 approximately 50%, but no lower than approximately 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 approximatly 50% reduced enzyme dose were randomly assigned in the two crossover treatment periods.

During each of the two treatment periods, the patients were instructed to maintain a daily diary for food records, abdominal symptoms, stool characteristics and the number of enzyme capsules taken each day for the three days at home. Patients then reported to the GCRC on the evening of the third day for 72 hours of stool collection (third stool collection). At the completion of the 72 hours of stool collection the patients was discharged from the GCRC.

The primary efficacy variable in the final protocol (April 3, 1998) was the percentage of fat excreted, later inversed to CFA in the study report. The secondary efficacy variable was CNA. Other efficacy variables included fat intake, protein intake, carbohydrate intake, energy, total fat excretion, stool weight and calculated kcal excreted in stool from fat. Additional variables included number of enzyme capsules (lipase dose) consumed per 24 hours.

The sample size was based on a crossover design using a two-sided t-test with a significance level of 0.05. A sample of 20 subjects would have 90% power to detect a difference of 6.5% in fat excretion between PANCRECARB® MS-8 and patients' usual EC enzyme. A total of 24 patients were needed to allow for a 17% dropout rate. Twelve patients were to be enrolled at each of the Cincinnati and Indianapolis site.

3.1.2.2 Patient Disposition, Demographic and Baseline Characteristics

This study was conducted over a more than 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 treatment period and was excluded from the efficacy analysis. That left 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. For three subjects (002, 003, 009) at the Cincinnati site, the investigators felt the Carmine red stool dye marker failed because of its color and so repeated stool collection in their second treatment period. Two patients (004, 009) at the Indianapolis site had repeated studies as outpatients based on the investigators assessment of inadequacy of stool collections or possible lab error in specimen handling. The sponsor decided these repeated studies were not considered major protocol deviations although it was not specified in the final protocol. One patient (011) at the Indianapolis site was non-compliant to 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 repeated 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 3.2.1 below.

Table 3.2.1. 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: Reviewer's Table

3.1.2.3 Statistical Methodologies

There was no SAP prepared 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 a method by Grizzle for analyzing crossover studies. 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 significance level.

3.1.2.4 Results and Conclusions

Table 3.2.2 below presents the analysis results on the efficacy variables for both ITT and PP population. The outcomes for two populations are different and the significance could be found in the PP population but not the ITT population.

Table 3.2.2. Efficacy Results

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

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

Due to the fact that this study was open-label, had no washout period between two crossover treatment periods, used repeated treatment assessments, and had changes in the analysis plan, the results cannot reliably support an efficacy claim.

3.2 Overview of Safety

A total of nine clinical studies were submitted within this NDA, which provided supportive evidence of the safety of PANCRECARB® in the treatment of patients with EPI. The primary safety measurement in all PANCRECARB® clinical studies was assessment of AEs. Safety variables assessed also included sign and symptoms of malabsorption (e.g., abdominal discomfort, flatulence, stool frequency and consistency).

The sponsor reported that a total of 267 subjects were available for inclusion in efficacy analyses; however, five of those subjects did not receive PANCRECARB®. Of the 262 safety subjects treated with PANCRECARB®, the sponsor reported that 77 (29%) experienced 148 AEs. Of these, 36 (14%) subjects experienced at least one AE that was possibly, probably or definitely related to treatment.

The sponsor further indicated that the most commonly reported AE (greater than 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 seven reports of severe abdominal pain, six of which were considered related to treatment. Other AEs reported for subjects treated with PANCRECARB® included upper abdominal pain and headache (eight each), diarrhea and flatulence (seven each), abdominal distension and frequent bowel movements (six each). Three patients experienced four AEs that were considered serious by the study investigators. None of the serious AEs (SAEs) were considered related to PANCRECARB® treatment. Four deaths were recorded during the two-year long-term study (091897) period and the sponsor claimed that none of them were attributed to the use of PANCRECARB®. No other deaths were reported during any other study with PANCRECARB®.

Overall, the sponsor reported 22 subjects (8%) from the total safety population discontinued for reasons attributed to AEs, 18 of those 22 were receiving PANCRECARB®. The majority of the AEs were gastrointestinal in nature.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section discusses the results for the pivotal Study 06-001. The sponsor did not perform any subgroup analyses except for the age group (adults and children) described in Section 3.1.1. Based on Table 3.1.2, the patients enrolled were unbalanced in terms of gender and race. Moreover, this study had very small sample size. Therefore, efficacy analyses in the gender and race subgroups are limited, and not further discussed in this review.

It is usually recognized that the PEP treatment effect has a linear relationship with placebo CFA. In other words, the lower the CFA under placebo, the higher the treatment effect (larger increase in CFA under the active treatment). A simple regression model on the data from Study 06-001 also shows this relationship (slope estimate = -0.725 and $p < 0.0001$).

Table 4.1 below shows the efficacy results for two subpopulations based on the CFA following placebo (CFA < 40% and CFA ≥ 40%) and the difference in treatment effect between these two subgroups is noticeable. Using the t-tests, these results did not change, as was the case for the whole completed-treatment population.

Table 4.1. Comparison of CFA Stratified by Placebo CFA (%, Completed-Treatment Population) for Study 06-001

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 - Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
Placebo CFA < 40%				
Overall (n = 9)	76.990	25.298	51.692[a]	(38.390, 64.994)
Children (n = 5)	73.629	24.871	48.758[a]	(29.947, 67.570)
Adults (n = 4)	80.350	25.725	54.625[a]	(35.813, 73.437)
Placebo CFA ≥ 40%				
Overall (n = 12)	86.676	61.018	25.658[a]	(18.008, 33.307)
Children (n = 5)	86.607	62.752	23.855[b]	(12.075, 35.635)
Adults (n = 7)	86.745	59.284	27.461[a]	(17.529, 37.293)

[a] $P < 0.001$
[b] $P = 0.0013$
Source: Reviewer's Table

The homogeneity among the study sites was also investigated by this statistical reviewer. The largest site had six patients while the smallest had only two. There was no visible impact from site on the outcomes.

5. SUMMARY AND CONCLUSIONS

From the pivotal Study 06-001, it can be concluded that there is an overall treatment effect of PANCRECARB® MS-16 on the primary efficacy endpoint of CFA. However, whether or not PANCRECARB® MS-16 would improve CFA for the patients with CFA levels greater than 80% under placebo or no treatment is inaccessible due to lack of data. The other controlled Study 97-001-1B lacked statistical rigor to support any efficacy claims of PANCRECARB® MS-8. There were no other controlled clinical studies submitted in support of demonstration of efficacy and safety of PANCRECARB® MS-8 (b) (4)

APPENDIX

Table A.1. T-test on Comparison of CFA by Sequence and Period (%, Completed-Treatment Population) for Study 06-001

Age Group	Means		Mean Difference (PANCRECARB® MS-16 - Placebo)	95% CI of Difference	
	PANCRECARB® MS-16	Placebo		Two independent sample t-test	Paired t-test
Sequence 1 (PANCRECARB® → Placebo)					
Overall (n = 12)	83.517	44.542	38.975	(26.261, 51.689)	(28.055, 49.895)
Children (n = 6)	81.633	41.317	40.317	(16.628, 64.005)	(21.047, 59.587)
Adults (n = 6)	85.400	47.767	37.633	(22.397, 52.869)	(19.205, 56.062)
Sequence 2 (Placebo → PANCRECARB®)					
Overall (n = 9)	81.411	47.933	33.478	(15.623, 51.333)	(19.478, 47.477)
Children (n = 4)	79.425	50.975	28.450	(-1.287, 58.187)	(1.105, 55.795)
Adults (n = 5)	83.000	45.500	37.500	(8.149, 66.852)	(12.778, 62.222)
Treatment Period 1					
Overall (n = 21)	83.517	47.933	35.583	(18.819, 52.348)	
Children (n = 10)	81.633	50.975	30.658	(0.106, 61.211)	NA
Adults (n = 11)	85.400	45.500	39.900	(15.784, 64.016)	
Treatment Period 2					
Overall (n = 21)	81.411	44.542	36.869	(23.818, 49.921)	
Children (n = 10)	79.425	41.317	38.108	(15.825, 60.391)	NA
Adults (n = 11)	83.000	47.767	35.233	(15.576, 54.891)	

Source: Reviewer's Table

Table A.2. Comparison of CNA (%, Completed-Treatment Population) for Study 06-001

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 - Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
Overall (n = 21)	79.986	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, 38.826)

[a] $P < 0.001$

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

Table A.3. Comparison of CFA and CNA (%, Completed-Treatment Population) with Data before Audit for Study 06-001

Age Group	Least Square Means		Difference (PANCRECARB® MS-16 - Placebo)	95% CI of Difference
	PANCRECARB® MS-16	Placebo		
CFA				
Overall (n = 21)	82.626	46.631	35.995[a]	(27.806, 44.184)
Children (n = 10)	81.155	46.524	34.631[a]	(22.789, 46.473)
Adults (n = 11)	84.096	46.737	37.359[a]	(26.152, 48.566)
CNA				
Overall (n = 21)	79.196	47.554	31.642[a]	(26.125, 37.158)
Children (n = 10)	78.821	44.608	34.213[a]	(26.237, 42.190)
Adults (n = 11)	79.570	50.500	29.070[a]	(21.521, 36.618)

[a] $P < 0.001$

Source: Reviewer's Table

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/s/

Freda Cooner
7/21/2009 02:14:10 PM
BIOMETRICS

Mike Welch
7/21/2009 03:18:56 PM
BIOMETRICS
Concur with review.

STATISTICS FILING REVIEW

NDA Number: 22-175 **Applicant: Digestive Care, Inc. (DCI)** **Stamp Date: 27-Oct-08**

Drug Name: PANCRECARB® pancrelipase **NDA/BLA Type: NDA**

On initial review of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).		X		Efficacy was only investigated for geriatric subgroups
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.		X		Safety datasets were submitted for each study individually with different formats
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		Such an investigation

				cannot be located

Background

Digestive Care, Inc., (DCI) has developed PANCRECARB® (pancrelipase) Capsules, a pancreatic enzyme replacement therapy (PERT) product, for the treatment of exocrine pancreatic insufficiency (EPI). DCI filed an Investigational New Drug (IND) application (#45,223) in April 1994 for its patented formulation of encapsulated enteric-coated buffered pancrelipase microspheres. The original IND was filed under the product name of [redacted] (b) (4) The tradename PANCRECARB® was filed to the US Patent and Trademark Office by DCI on June 19, 1995, and registered on March 11, 1997. DCI then amended IND #45,223 to change the product name to PANCRECARB® on July 15. 1999 (Serial #005). PANCRECARB® Capsules are available in three dosage strengths: MS-4, MS-8, and MS-16 (related to the labeled lipase potency of each dosage unit; i.e., 4,000, 8,000, and 16,000 USP units of lipase per capsule, respectively). DCI introduced PANCRECARB® MS-8 onto the US market in 1995, as a physician-prescribed PERT. Two additional dosage strengths, PANCRECARB® MS-4 and MS-16 were introduced onto the US market in 2000 and 2004, respectively.

DCI has had a number of meetings with the Division of Gastroenterology Products as follows:

June 23, 2005	Type B (Preclinical/Clinical) Meeting
October 19, 2005	Type C (CMC) Meeting
September 11, 2006	Type C (Preclinical/Clinical) Meeting
February 5, 2007	Type C (CMC) Meeting
October 31, 2007	Type B (Pre-NDA) Meeting

On November 26, 2007, Fast Track designation was granted for PANCRECARB® for the treatment of EPI. DCI subsequently submitted an amendment to IND #45,223 (Serial #055) dated April 17, 2008 containing a request to submit portions of the NDA for review before the complete NDA is submitted (i.e., rolling submission). Followed by the acceptance from the Division, DCI submitted the first reviewable unit of the PANCRECARB® NDA on June 20, 2008. Instead of originally proposed date of April 28, 2009, DCI submitted the remaining portions to complete the PANCRECARB® NDA on October 27, 2008.

This application is currently submitted under the provisions of 505(b)(1) of the Food, Drug and Cosmetic Act. However, approval/disapproval decision may rely on [redacted] (b) (4) information and/or published literature. If so, DCI would need to withdraw this NDA and resubmit under the provisions of 505(b)(2).

Datasets and study reports have been submitted in Common Technical Document (CTD) format to the EDR at: \\Fdswa150\nonectd\N22175\N_000.

Overview of studies

This PANCRECARB® NDA includes clinical data for [redacted] (b) (4) MS-8, and MS-16. The clinical bioavailability, efficacy and safety of PANCRECARB® have been supported by a total of 10 clinical studies, including over 270 subjects between the ages of 2 to 79 years. The table below [Table 2.7(1) in Section 2.7 Clinical Summary of the submission] summarizes the six controlled pivotal studies.

Study ID (study period)	Study Objective(s) Primary Endpoint(s)	Study Design and Type of Control (number of study centers / location)	Test Product(s)	Dosage Regimen	Number and Age Range of Subjects Evaluable (efficacy/safety)	Duration of PANCRECARB® Treatment Evaluated
CONTROLLED CLINICAL STUDIES PERTINENT TO THE CLAIMED INDICATION						
06-001 (2/2007-9/2007) NCT00432861	**Study Objective(s):** Demonstrate the efficacy and safety of PANCRECARB® MS-16 (pancrelipase), as compared to Placebo, for reduction of steatorrhea (as measured by 72-hour stool fat determinations) **Primary Endpoint(s):** Differences in the %CFA between the two study treatment periods	Randomized, double-blind, placebo-controlled, 2-way crossover (5 study centers / USA)	PANCRECARB® MS-16 and Placebo	PANCRECARB® dose was titrated to symptom control over a 7-10 day period. The dose established during this Dose Stabilization Period was the dose used for the remainder of the study during Treatment Periods 1 and 2.	21 / 24 Ages 8-43 years	7 days
97-001-1B (3/1997-8/2001) NCT00006063	**Study Objective(s):** Determine the safety and efficacy of PANCRECARB® MS-8 at ~50% reduced lipase dose in reducing fecal fat and nitrogen losses in patients with CF when compared with other EC enzyme supplements also at 50% reduced lipase dose **Primary Endpoint(s):**	Randomized, open-label, active-controlled, 2-way crossover (2 study centers / Cincinnati, OH; Indianapolis, IN)	PANCRECARB® MS-8 (DCI) and Creon® 20 (Solvay Pharmaceutical); Pancrease® MT-10 and MT-20 (Ortho/ McNeil); Ultrase® MT-12, MT-18 and MT-20 (Axcan/ Scandipharm)	Both PANCRECARB® and the patient's usual enzyme dose were 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 the 2 seven day treatment periods.	19 / 19 Ages 12-27 years	7 days

Study ID (study period)	Study Objective(s) Primary Endpoint(s)	Study Design and Type of Control (number of study centers / location)	Test Product(s)	Dosage Regimen	Number and Age Range of Subjects Evaluable (efficacy/safety)	Duration of PANCRECARB® Treatment Evaluated
	Differences in the %CFA between the two study treatment periods					
OTHER CONTROLLED CLINICAL STUDIES						
97-001-2 (11/1997-5/1998)	**Study Objective(s):** Determine the safety and efficacy of PANCRECARB® MS-8 at ~50% reduced lipase dose in reducing fecal fat and nitrogen losses in patients with CF when compared with other EC enzyme supplements **Primary Endpoint(s):** Difference in the %CFA and %CNA between the two study treatment phases.	Non-randomized, open-label, active-controlled, 1-way crossover (single center / Philadelphia, PA)	PANCRECARB® MS-8 (DCI) and Creon® 10 or 20 (Solvay Pharmaceutical)	Patients were administered their current enzyme at the usual lipase dose during Phase 1. At Phase 2, patients were switched to PANCRECARB® at a ~50% reduced lipase dose compared to the patient's usual lipase dose used in Phase 1.	6 / 6 Ages 4-17 years	7 days
092100 (2/2001-4/2002)	**Study Objective(s):** Determine the safety and efficacy of PANCRECARB® MS-8 in reducing diarrhea and malabsorption associated with highly active antiretroviral therapy (HAART) in HIV-positive patients **Primary Endpoint(s):**	Double-blind, randomized, placebo-controlled, 2-way crossover (single center / Somerville, NJ)	PANCRECARB® MS-8 and Placebo	2 capsules per meal and 1 capsule per snack.	11 / 13* Ages 28-55 years * 14 subjects were enrolled in the study, but one discontinued due to non-compliance and no study medication was consumed.	7 days

Study ID (study period)	Study Objective(s) Primary Endpoint(s)	Study Design and Type of Control (number of study centers / location)	Test Product(s)	Dosage Regimen	Number and Age Range of Subjects Evaluable (efficacy/safety)	Duration of PANCRECARB® Treatment Evaluated
	Reduction in the frequency of diarrhea					
020296[a] (9/1996-12/1996)	**Study Objective(s):** Compare the efficacy and safety of a new pancreatic enzyme preparation, PANCRECARB® MS-8 (EC-low-buffered pancrelipase containing 1.4 mEq of buffer/capsule) with a positive control, Cotazym® ECS-8 (ECnon-buffered pancrelipase) **Primary Endpoint(s):** Differences in the %CFA between the two study treatment periods	Double-blind, randomized, active-controlled, 2-way crossover (single center / Toronto, Canada)	PANCRECARB® MS-8 low bicarbonate (DCI) and Cotazym® ECS-8 (Organon)	Both PANCRECARB® and the patient's usual enzyme (Cotazym®) were administered at the same dose during both treatment periods. The dose was based on the patient's Cotazym® dose.	21 / 22 Ages 8-41 years	14 days
111395[a] (2/1996-12/1996)	**Study Objective(s):** Determine if a reduced dose of pancreatic enzyme is able to improve fat absorption in CF patients with documented pancreatic insufficiency **Primary Endpoint(s):** Differences in the %CFA between the	Non-randomized, open-label, active-controlled, 1-way crossover (single center / Cincinnati, OH)	PANCRECARB® MS-8 low bicarbonate (DCI) and Creon® 20 (Solvay Pharmaceutical); Pancrease® MT-16 (Ortho/ McNeil); Ultrase® MT-20 (Axcan/ Scandipharm); Cotazym® ECS-8	Patients were administered their current enzyme during Phase 1. At Phase 2, patients were switched to PANCRECARB® equal to their lipase dose from Phase 1, for 2 weeks, and then an additional 2 weeks (Phase 3) of PANCRECARB® at 2/3	6* / 10 Ages 8-16 years * 7 subjects completed the protocol, but 1 subject did not provide stool fat collections from Phase 3.	14 days at 100% usual dose, 14 days at 2/3 usual dose

Study ID (study period)	Study Objective(s) Primary Endpoint(s)	Study Design and Type of Control (number of study centers / location)	Test Product(s)	Dosage Regimen	Number and Age Range of Subjects Evaluable (efficacy/safety)	Duration of PANCRECARB® Treatment Evaluated
	study treatment phases		(Organon)	of the Phase 1 lipase dose.		

[a] The (b) (4) PANCRECARB® (pancrelipase) MS-8 drug product used in these studies was formulated with a (b) (4) carbonate/bicarbonate buffering, which differs from the (b) (4) buffering used in the product formulation from 1997 to the current date.

Review issue

The sponsor has submitted the analysis datasets for this NDA in accordance with current eCTD guidance. We should recommend that the sponsor provide electronic analysis programs as well.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Freda Cooner
11/21/2008 02:10:44 PM
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Mike Welch
11/21/2008 06:25:26 PM
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