CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-523
Priority or Standard	Standard
Submit Date(s)	June 23, 2009
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Reviewer Name(s)	Ali Niak, M.D.
Through	Anil Rajpal, M.D. Clinical Team Leader
Review Completion Date	April 12, 2010
Established Name	Pancrelipase Delayed-Release Capsules
(Proposed) Trade Name	PANCREAZE
Therapeutic Class	Pancreatic Enzyme Product
Applicant	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Formulation(s)	For oral administration
Dosing Regimen	Not to exceed 2,500 USP lipase units/kg/meal or 10,000 USP lipase units/kg/day
Indication(s)	Exocrine pancreatic insufficiency
Intended Population(s)	Patients with exocrine pancreatic insufficiency

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends an Approval (AP) action.

From a clinical perspective, the safety and efficacy of Pancreaze have been established for the treatment of patients with exocrine pancreatic insufficiency (EPI) due to Cystic Fibrosis (CF) or other conditions. The pivotal study PNCRLPCYS3001 demonstrated the short-term efficacy and safety of Pancreaze for patients with CF and EPI, ages seven years to adult. The short-term safety and efficacy information obtained from Study 20-101 was supportive of the treatment with Pancreaze in pediatric patients with CF and EPI, ages 6 to 30 months. In the opinion of this Reviewer, the clinical data submitted in the NDA are adequate to label Pancreaze for patients with EPI due to CF or other conditions.

1.2 Risk Benefit Assessment

The efficacy and safety of Pancreaze was demonstrated by the results of two short-term trials (PNCRLPCYS3001 and 20-101).

The pivotal study, PNCRLPCYS3001, was a multi-center, double-blind, placebo-controlled, randomized withdrawal study to evaluate the efficacy and safety of Pancreaze compared with placebo in 40 patients with CF and EPI between the ages of 8 and 57 years old. Patients received Pancreaze at individually titrated doses (not to exceed 2,500 lipase units per kilogram per meal) for 14 days (open label period) followed by randomization to Pancreaze or matching placebo for 7 days of treatment (double-blind withdrawal period); only patients with coefficient of fat absorption (CFA) $\geq$80% in the open label period were randomized to the double-blind withdrawal period. The primary efficacy endpoint was the change in CFA from the open label period to the end of the double-blind withdrawal period. There was a clinically meaningful and statistically significant difference in the change in CFA in Pancreaze treated patients versus patients treated with placebo.

The supportive study, 20-101, was a randomized, investigator-blinded, dose-ranging study of Pancreaze in 17 patients with CF and EPI between the ages of 6 and 30 months old. A primary efficacy endpoint was the change in the coefficient of fat absorption (CFA) measured from Visit 2 (Randomization) to Visit 3 (End of Study). The results suggested that Pancreaze was equally effective at all doses based on change in CFA.

There were no deaths in either study. The adverse events (AEs) observed during the studies were mostly in the gastrointestinal system; these events may be symptoms of the underlying disease and may not be adverse reactions to the pancreatic enzyme product (PEP). There were no serious adverse events during the two studies.

PEPs are currently used by both adult and pediatric patients for the treatment of EPI due to numerous causes.

Although the clinical development program for Pancreaze did not include patients less than six months old, the Division is not requesting that the Sponsor conduct any additional clinical trials to include patients younger than six months 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.

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 Pancreaze 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 should not be less frequent than 18 months, three years, and seven years after the REMS is initially approved. Each assessment must evaluate the extent to which the elements of the REMS are meeting the goals of the 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 Pancreaze Delayed-Release Capsules.

Therefore, based on appropriate scientific data, the Agency has determined that 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 Pancreaze Delayed-Release Capsules in the US and to assess potential risk factors for the event.

Final Protocol Submission:	June, 2011
Study Completion Date:	January, 2022
Final Report Submission:	August, 2022

2. A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Pancreaze Delayed-Release Capsules.

Final Protocol Submission:	June, 2011
Study Completion Date:	December, 2021
Final Report Submission:	September, 2022

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

1.4 Recommendations for Postmarket Studies/Clinical Trials

The following post-marketing study commitments (PMCs) will be performed:

(1) Initiate and complete the proposed studies (04020298 & 04020299) that evaluate the stability of Pancreaze under conditions of use.

Final Report Submission: by September 30, 2011

(2) Re-evaluate the acceptance criteria for the protease and amylase assays after more experience is gained with the Pancreaze manufacturing process. After 50 drug product lots are manufactured, specifications will be re-evaluated and adjusted to reflect manufacturing history and capability.

Final Report Submission: by March 31, 2013

(3) Develop and validate an infectious assay for PCV1.

Final Report Submission: by January 31, 2011

(4) Establish lot release specifications for PCV1.

Final Report Submission: by July 31, 2011

(5) Perform additional monitoring of viral load entering the manufacturing process. The control program will include monitoring for human pathogenic viruses by qPCR. An appropriate control strategy will then be implemented.

Final Report Submission: by July 31, 2011

(6) Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. Revise the assays, and submit assay validation data, together with acceptance criteria.

Final Report Submission: by July 31, 2011

(7) Perform in vitro studies to determine the feasibility of administering the contents of PANCREAZE (pancrelipase) Delayed-Release Capsules through a gastrostomy tube.

2 Introduction and Regulatory Background

Exocrine pancreatic insufficiency (EPI) typically results from chronic loss of pancreatic tissue due to a number of underlying diseases. The most common cause of EPI in children is cystic fibrosis; the most common cause of EPI in adults is chronic pancreatitis. Cystic fibrosis (CF) is a congenital disease characterized by the production of abnormally viscous mucus secretions, engendering pathologic change which causes respiratory and gastrointestinal dysfunction, thereby affecting life expectancy. One of the principal gastrointestinal effects of CF is the deficient production of pancreatic enzymes which are essential for digestion; this, in turn, leads to malnutrition and ultimately worsens the overall prognosis of the patient. Chronic pancreatitis (CP) is one of the most prevalent pancreatic insufficiency diseases of adults and results from a decrease in pancreatic enzyme secretions to less than 10% of the levels observed in healthy adults. The condition is most frequently associated with alcoholism, although chronic pancreatitis leading to chronic pancreatic insufficiency can result from many etiologic factors, including biliary tract disease, postoperative trauma, vascular disease, ductal obstruction from neoplasm, and post-gastrointestinal bypass surgery. There are many other causes, such as pancreatectomy.

Steatorrhea (excess fat in the stool) is a primary sign of EPI. EPI can be managed by providing the necessary pancreatic enzymes to the duodenum (i.e., lipases, proteases, and amylases) to facilitate digestion of macronutrients (i.e., fats, carbohydrates and proteins).

2.1 Product Information

The investigational agent studied in this application is Pancreaze, a porcine-derived pancreatic enzyme product (PEP) for oral administration. Pancreplipase is the active ingredient and it is a concentrated porcine extract comprised of the following pancreatic enzymes: liapse, amylase, and protease.

Pancreaze is a combination of porcine-derived lipases, proteases, and amylases. Pancreaze delayed-release enteric-coated microtablets are currently marketed in the United States (U.S.) without an approved NDA under the name “Pancrease MT.” On April 28, 2004 (69 Federal Register [FR] 23410), the FDA announced that all pancreatic enzyme products (PEPs) are new drugs for which an NDA must be approved by April 28, 2008, for continued marketing. In October of 2007, the FDA extended the date by which sponsors must have approved NDA’s to April 28, 2010 (72 Federal Register 60860).

Pancreaze delayed-release capsules contain enteric-coated microtablets of porcine pancreatic enzyme concentrate, predominantly lipase, amylase, and protease. Pancreaze has been used in diseases or conditions involving EPI, such as CF, CP, post-pancreatectomy, post-gastrointestinal

bypass surgery, or ductal obstruction due to neoplasm, which disrupts the normal digestion of nutrients.

The Sponsor is proposing that Pancreaze be indicated for the treatment of EPI due to CF or other conditions.

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. 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. In April 2006, the Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products was published (PEP Guidance)[1]. Each PEP requires an approved new drug application (NDA) for continued marketing; according to the latest Federal Register notice, all PEPs must have had an NDA submitted by April 28, 2009. There are two PEPs currently marketed (Creon and Zenpep) that have been approved by the FDA.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in Pancreaze is pancrelipase. Pancrelipase is presently widely available as enteric coated (EC) and non-EC formulations from several different manufacturers; it should be noted that the formulations are not interchangeable. The FDA is requiring that all PEPs be marketed under an approved NDA by April 28, 2010, thereby, preventing any PEPs from being available without a prescription. Please refer to Section 2.5 for a complete description of the regulatory history.

2.4 Important Safety Issues With Consideration to Related Drugs

PEPs were never evaluated for safety and efficacy under an NDA. PEPs have been available prior to the Food Drug and Cosmetic Act of 1938. Concerns regarding the variability in potency and safety led to a series of regulatory decisions establishing that PEPs were not generally recognized as safe and effective (GRAS and GRAE, respectively) in the 1990's. Substantial irregularities in potency would lead patients to be either over-dosed or under-dosed, raising different safety and efficacy concerns.

Fibrosing colonopathy (FC) is the most serious safety concern with PEP administration that has been reported mainly in young children with CF who are being administered delayed-release PEP formulations. The exact etiology of FC is not known, but studies have shown that the majority of cases of FC have been associated with high-dose use of pancreatic enzyme replacement in the treatment of cystic fibrosis patients. Caution has been advised when doses of Pancreaze exceed 10,000 lipase units/kg of body weight per day or 2,500 lipase units/kg of body weight per meal.

[1] Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs. April 2006 (http://www fda.gov/cder/guidance/6275fnl.htm)

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).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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

During an End of Phase 2 meeting (January 16, 2008)[2], the Sponsor proposed a randomized withdrawal design based on a publication by Stern et al.[3] The Sponsor inquired in that meeting if the study design was sufficient to differentiate Pancreaze from placebo and to establish efficacy in terms of coefficient of fat absorption (CFA). The Division responded that the general design of the proposed study was reasonable.

The original IND submission (IND 74,893) was received in May 2008 for Pancreaze (pancrelipase) for EPI. The study design was agreed upon in the clinical review of the pivotal study protocol.[4]

Overall, PEPs were initially marketed in the U.S. in the 1920's, prior to the Food Drug and Cosmetic Act of 1938. PEPs were never evaluated for safety and efficacy under an NDA but they have been widely available throughout the world (including the U.S.) as nutritional supplements.

On July 15, 1991, the Agency published a Notice of Proposed Rulemaking in the Federal Register (FR) secondary to concerns regarding variability in potency; it was also established that PEPs were not considered as GRAS (Generally Recognized As Safe) and GRAE (Generally Recognized As Effective). The Agency declared that all PEPs be considered new drugs requiring an NDA for continued marketing. In April 2004, the Agency published a Notice of Requirement in the Federal Register for NDA approval of all PEPs within the next four years. The deadline was initially set for April 28, 2008; however, in October of 2007, the deadline was extended until April 2010 with the requirement that all PEPs must have an open IND by April 28, 2008.

The Guidance for Industry; Exocrine Pancreatic Insufficiency Drug Products was published[5] in April 2006, thereby, stating that animal- (porcine- and bovine-) derived PEP NDA applications would be submitted as 505(b)(2) applications. The sponsors were allowed to have a limited clinical development program that could include short-term studies in order to establish safety and efficacy in these submissions. For PEP applications, these abbreviated clinical development

[2] Meeting minutes dated 01/25/08
[3] Stern et.al., *American Journal of Gastroenterology* 2000; 95(8): 1932-8.
[4] Medical Officer Review of protocol PNCRLPCYS3001 by Joanna Ku (IND 74,893)
[5] 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.

programs have been deemed acceptable because the assumptions made about the safety and efficacy of these products are based on a large body of safety and efficacy information available in the medical literature. Additionally, the current Cystic Fibrosis Foundation (CFF) consensus statement considers PEPs to be the standard of care for Exocrine Pancreatic Insufficiency (EPI) due to CF and other causes.

2.6 Other Relevant Background Information

The application was presented to the Pediatric Research Committee (PeRC) on March 31, 2010; there were also additional clarifications and discussion with the Division subsequent to the meeting. There will be a waiver for the pediatric population from birth to one month of age; there will be a deferral for development of an age-appropriate formulation for patients less than 12 months of age. Studies will be considered as being completed for ages greater than 12 months to 17 years because 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 this population.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the submission was organized in a clear and concise fashion. The information was readily available.

3.2 Compliance with Good Clinical Practices

The study was conducted in accordance with the protocol, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP) guidelines, Food and Drug Administration (FDA) regulations, ethical principles that have their origin in the Declaration of Helsinki, and all applicable local regulations, whichever offered the greater protection for the subject.

3.3 Financial Disclosures

Johnson and Johnson Pharmaceutical Research and Development, L.L.C. has disclosed financial arrangements with clinical investigators, as recommended in the FDA guidance for industry.

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 Reviewer, Howard Anderson, Ph.D. His recommendations are for an approval action. Please see these reviews for more detailed information.

4.2 Clinical Microbiology

This NDA is recommended for approval by the Microbiology Reviewer, Bryan S. Riley, Ph.D. Please refer to the Microbiology Review for more detailed information on the microbiology data.

4.3 Preclinical Pharmacology/Toxicology

No non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA. This is consitent with the recommendations in the PEP Guidance. However, it should be noted the sponsor provided toxicity studies and embryo-fetal developmental studies of pancrelipase; the pharmacology/toxicology reviewer commented that it is uncertain whether the drug substance used in these studies is comparable to the drug substance in Pancreaze. Please see the Nonclinical Pharmacology Review (by Ke Zhang, Ph.D.) for more detailed information on the nonclinical information relevant to this NDA submission.

4.4 Clinical Pharmacology

Clinical pharmacology data have been extensively reviewed by the Office of Clinical Pharmacology (OCP). The reviewer noted that from a clinical pharmacology standpoint, the application is acceptable provided agreement can be reached on the labeling with the sponsor.

Results of Study PNCRLPYS-1001, the *in vivo* intubation study, are provided in the Clinical Pharmacology Review by Lanyan Fang. However, the clinical pharmacology reviewer noted that the bioavailability study using the intubation procedure is considered unreliable for assessing the *in vivo* delivery of pancreatic enzymes to the duodenum. It was also noted that the bioavailability study is not a required study for the NDA approval. Please refer to the Clinical Pharmacology Review (by Lanyan Fang, Ph.D.) for detailed information relevant to this NDA submission.

4.4.1 Mechanism of Action

Pancreaze 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 Studies/Clinical Trials

There were three clinical studies conducted in the Pancreaze clinical development program to support the approval of this NDA: two clinical studies to evaluate the safety and efficacy (the pivotal study PNCRLPCYS3001 and the supportive study 20-101) in patients with severe exocrine pancreatic insufficiency. There was also a clinical pharmacology study (PNCRLP-CYS-1001). Please refer to Table 1 for a listing and summary of these studies.

Table 1. Table of Studies/Clinical Trials

Study	Phase	Characteristics
PNCRLPCYS3001	3	Pivotal study: Randomized, placebo-controlled, double-blind (withdrawal) study; evaluated the efficacy and tolerability of Pancreaze versus placebo in subjects 7 to 60 years old with CF-dependent EPI
20-101	2	Supportive Study: Randomized, parallel group, investigator-blinded pilot study to evaluate safety, palatability, and efficacy of Pancreaze microtablets to improve steatorrhea in infants and toddlers ages 6 to 30 months with a history of CF-related pancreatic insufficiency
PNCRLP-CYS-1001	1	Clinical Pharmacology Study: Randomized, open-label, single-dose, crossover study to evaluate intra-duodenal enzyme delivery of Pancreaze in subjects 18 to 85 years of age with severe EPI

A detailed discussion of the pivotal and supportive studies is provided in the following sections.

5.2 Review Strategy

The two clinical studies, PNCRLPCYS3001 (pivotal study) and 20-101 (supportive study), submitted to this application were reviewed in detail.

The majority of time was spent reviewing the pivotal study, PNCRLPCYS3001; efficacy of Pancreaze was established from this randomized, double-blind, placebo-controlled study. Study 20-101 was a randomized, parallel group, investigator-blinded study to evaluate safety and efficacy of Pancreaze microtablets to improve steatorrhea in infants and toddlers ages 6 to 30 months with a history of CF-related pancreatic insufficiency.

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 Pancreaze was consistent with the PEP Guidance.

5.3 Discussion of Individual Studies/Clinical Trials

Study PNCRLPCYS3001

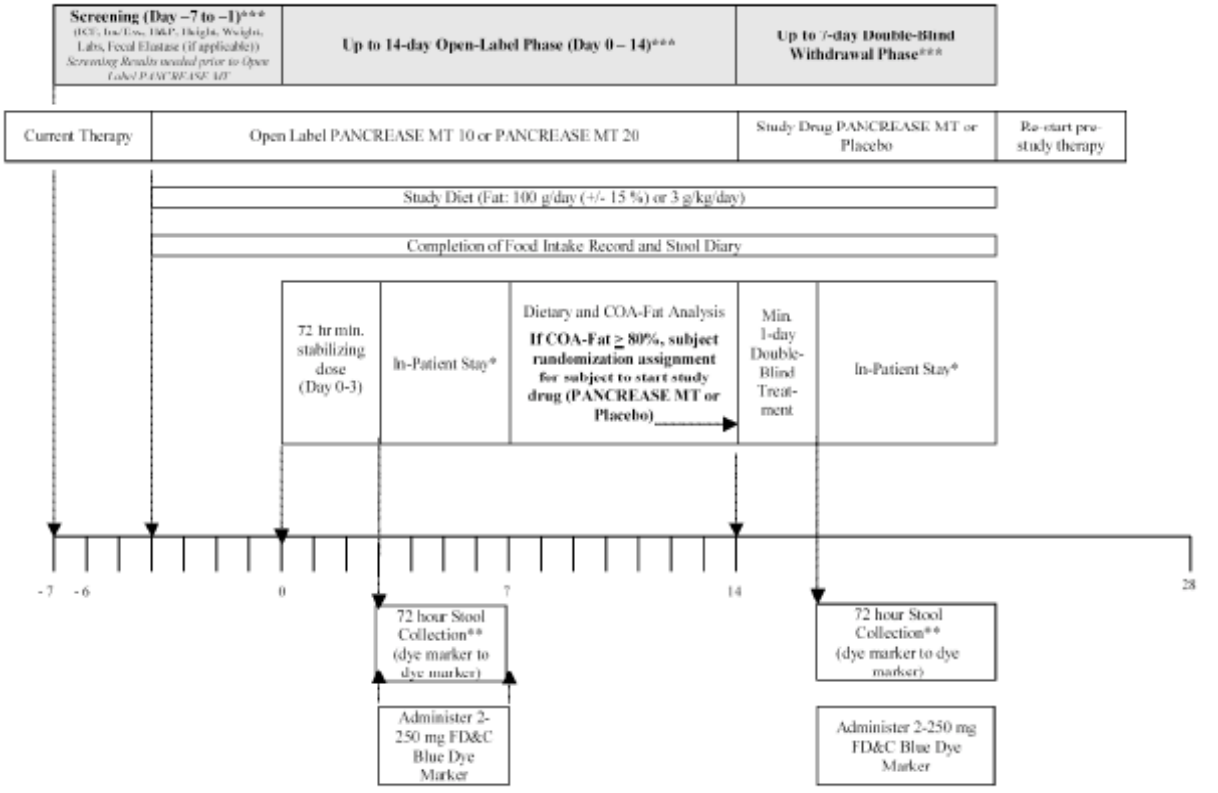
The Phase 3 Study PNCRLPCYS3001 was a randomized double-blind (withdrawal), placebo-controlled, multicenter study consisting of 3 phases: a 7-day screening phase, an up to 14-day open-label (run-in) phase, and an up to 7-day randomly assigned, placebo-controlled, double-blind (withdrawal) phase. The initial (screening) dose of Pancreaze was based on the average dose of pancreatic enzyme replacement therapy (PERT) taken for the 3 days immediately before entry into the study in combination with a high-fat diet. This PERT was continued until all screening test results were received and the subject met all inclusion/exclusion criteria. During the open-label phase, subjects discontinued the current PERT and started Pancreaze 10.5 or Pancreaze 21 treatment, which was adjusted to accommodate a high-fat target diet and to optimize digestion based on clinical signs and symptoms within the recommended ranges of pancreatic enzyme therapy as recommended by the Cystic Fibrosis Foundation. When an optimal dose was reached and maintained for at least 2 days, as evidenced by the maintenance of stable clinical symptoms, and after at least 3 days of the high-fat diet, subjects began an inpatient 72-hour open-label stool collection period, during which time their high-fat diet was strictly controlled. Subjects who qualified for randomization (based on results of the fecal fat analysis) were randomly assigned (1:1) to receive placebo or Pancreaze capsules during the double-blind phase. After a minimum of 1 day of double-blind treatment, subjects began a 72-hour inpatient stool collection period. Double-blind treatment was to range from 4 to 7 days, depending on the gastrointestinal transit time determined by orally ingested stool markers.

Approximately 40 adult (≥18 to 60 years old) or children/adolescent (7 to <18 years old) who required PERT to control clinical symptoms of EPI and steatorrhea were to be enrolled in this study. Fifty-four subjects were screened for entry into the study, and 5 of these subjects failed screening procedures. The remaining 49 subjects were enrolled; one subject withdrew consent

and was discontinued from the study prior to receiving open-label study drug. The remaining 48 subjects entered the Run-in Phase of the study and received open-label study drug. Eight of these subjects discontinued during the open-label phase and were excluded from the randomization; the remaining 40 subjects were randomized in a 1:1 fashion to receive either Pancreaze or placebo. All 40 subjects completed the study.

During the open-label phase, subjects were administered Pancreaze 10.5 or Pancreaze 21 treatment until an optimal dose was reached and maintained for at least 2 days, as evidenced by the maintenance of stable clinical symptoms, and after at least 3 days of the high-fat diet. Double-blind treatment was to range from 4 to 7 days, depending on the gastrointestinal transit time determined by orally ingested stool markers. The overall study design is represented graphically in the figure below.

Figure 1. Study PNCRLPCYS3001 Design



* Exact time of period depends on the gastrointestinal transit time of the subject as marked by the appearance of the blue dye marker in stool.
** All subsequent stools after the administration of the blue dye marker will be collected and observed for the appearance of blue dye. The first stool marked with blue dye is not to be saved for analysis, but all subsequent stools are saved. The stool collection period may exceed 72 hours depending of the appearance of the stool dye markers.
*** Subject will begin taking PANCREASE MT doses for the remaining days of the screening period after all screening test results have been received and reviewed. Subject must also discontinue any current PERT therapy.

NOTE: A visit window of +/- 3 days will be allowed for each study phase.

(from page 16 of the Clinical Study Report from Study PNCRLPCYS3001)

Table 2. Time and Events Schedule for Protocol PNCRLPCYS3001

	Screening (Days –7 to –1) *		Up to 14-day Open-Label (Run-in Phase)[a] *		Random Assignment[b]	Up to 7-day Double-Blind Withdrawal Phase[c, *]			End-of-Study/ Early Withdrawal[d]
	Eligibility Screening Day -7	6 days PANCREASE MT dose Day –6 - Day –1 (±3 days)	72-hr min.[a]	Inpatient 72-hr stool collection	If COA Fat ≥80%	Subjects on Double-Blind Treatment for Minimum of 1 day before Inpatient Treatment	Inpatient 72 hr stool collection		
Assessments	←Maintain high-fat diet throughout→								
Visits:	1			2	2b		3		4
Screening									
Informed Consent	X								
Inclusion and exclusion criteria	X								
Medical history	X								
Physical examination	X								X
Weight	X			X X X			X X X		X
Height	X								X
Administrative									
Study drug administration[e,f]		X	X	X X X	X	X	X X X		
Random assignment					X				
Dispense double-blind medication supply					X				
Dispense diaries	X								
Confinement to study site				X X X			X X X		
Safety									
Vital signs[g]	X								X
Clinical laboratory tests[h]	X								X
Uric acid[i]	X								X
Serum pregnancy test for females of childbearing potential	X								
Adverse events	←throughout→								
Concomitant therapies	←throughout→								
Efficacy									
Telephone monitoring[j]	←throughout→								
Stool collection	X[k]			X X X			X X X		
Nutrition diary	←throughout→								
Stool diary	←throughout→								
(COA-fat)					X			X	
(COA-protein [nitrogen])					X			X	
CGI-S									X
CGI-C									X
GAC									X

Abbreviations: Hr = hour; CGI-S Clinical Global Impression-Severity; CGI-C Clinical global impression –change; GAC = Global Assessment of Change; MT = microtablets.

* Indicates a visit window of ±3 days was allowed during the screening, open-label, and double-blind phases.

[a] At screening, subjects were instructed to adjust the number of capsules per meal (or snack) to optimize digestion based on clinical signs and symptoms. Subjects began taking PANCREASE MT doses for the remaining days of the screening phase after all screening test results were received and reviewed and they had discontinued any current PERT therapy. When an optimal dose was reached and maintained for at least 2 days and after at least 3 days on the high-fat diet, subjects began an inpatient 72-h stool collection, during which time the high-fat diet was strictly controlled. NOTE that the number of days required to reach an optimal dose may have included the days of PANCREASE MT dosing in the screening phase and extended into the first days of the open-label phase.

[b] Eligible subjects (subjects with a COA-fat of ≥80% after open-label treatment and who maintained a controlled high-fat diet for at least 6 days continued the high-fat diet and were randomized (1:1) to placebo or PANCREASE MT capsules at the same number of capsules taken at the end of the open-label phase.

[c] After a minimum of 1 day of double-blind treatment, subjects began a 72-h inpatient stool collection. Double-blind treatment ranged from 4 to 7 days, depending on gastrointestinal transit time determined by orally ingested stool markers (food dye).

[d] End-of-study/early-withdrawal assessments were performed for each subject at the end of the stool collection period (before discharge from the study center) in the double-blind (withdrawal) phase or upon early withdrawal.

[e,f] During the screening phase the average of 3 days intake of enzyme dose was used to identify the target PANCREASE MT dose for the open-label phase. Subjects (or their parents or legal guardians) self-administered study drug during outpatient periods in the screening, open-label, and randomized, double-blind (withdrawal) phases. During stool collection periods, study drug was administered at the inpatient site.

[g] Vital signs included oral temperature, pulse and respiratory rate, and diastolic and systolic blood pressure. Blood pressure and pulse was measured when a subject was in the sitting position after a 5-minute rest.

[h] Clinical laboratory tests included clinical chemistry, hematology, and urinalysis testing and fecal elastase, if needed.

[i] Uric acid concentrations were determined from blood samples obtained on the first day of screening and at the end-of study early-withdrawal visit. Uric acid at screening and end-of-study was part of the chemistry panel.

[j] Telephone contact was made with subjects on a daily basis to review diet intake and the monitoring of adverse events.

[k] A fecal elastase test (<100 µg fecal elastase/gram stool) of CF-related PI was to be available within 3 months before screening. If results were available or were older than 3 months, a fecal elastase test was performed during the screening phase.

(from pages 26 & 27 of the Clinical Study Report from Study PNCRLPCYS3001)

Study 20-101

This study was a phase II, randomized, investigator-blinded, parallel-group, pilot study, conducted in 5 European CF centers that evaluated preliminary safety, palatability and efficacy of Pancreaze in infants and toddlers ages 6 to 30 months with CF. The study consisted of two phases, an open-label run-in phase (Days 1-6), and a randomized phase (Days 6-11). During the open-label run-in phase, Pancreaze 375 units lipase/kg/meal was administered for 5 days and stools were collected during the last 72 hours. Subjects were then randomly assigned for 5 days to one of four treatment groups in a 1:1:1:1 ratio: a single-dose each of Pancreaze 375 units

lipase/kg/meal, 750 units lipase/kg/meal, 1125 units lipase/kg/meal, or 1500 units lipase/kg/meal and for a maximum of 5 meals per day. Stool was collected during the last 72 hours of the run-in and randomization phases and was quantitated for fecal fat and protein (nitrogen) content. Dietary intake for the duration of the stool collection was recorded for the calculation of CFA. At specified visits during the study, severity of illness, improvement of CF symptoms from baseline, effectiveness, and palatability were assessed. The number of subjects who were discontinued during the open-label run-in and randomization phases was provided together with a breakdown of the primary reasons for premature discontinuation.

Approximately 20 subjects were planned to be enrolled, 18 subjects were enrolled, 17 were randomized and 16 completed the study. Please refer to the table below for the overall study design.

Table 3. Study 20-101 Design

Schedule of Assessments	Visit 1	Run-In Period	Visit 2	Randomized Period	Visit 3
Days	1	1-6 (120 hours inclusively)	6	6-11 (120 hours inclusively)	11
Informed consent	X				
Medical history	X				
Physical examination	X		X		X
Review of historical COA	X				
Weight	X		X		X
Vital signs	X		X		X
Length	X				X
Head circumference	X				X
Subject randomized			X		
Concomitant medication history	X	X	X	X	X
Adverse event		X	X	X	X
72-hour stool collection		X		X	
72-hour stool collection drop-off			X		X
MTG substrate breath test			X		X
Global assessment of severity of illness subscale	X		X		X
Global change subscale			X		X
Global assessment of effectiveness			X		X
Global assessment of palatability (once daily)		X		X	
Phone call		X		X	
Study drug dispensed	X		X		
Study medication administration		X		X	
Dispense diary	X		X		
Review diary			X		X
Collect unused drug			X		X
Collect diary			X		X

(from page 38 of the Clinical Study Report of Study 20-101)

It should be noted that the term "USP units" was incorrectly used in the 20-101 Study Report as per the Sponsor in an addendum to the Study Report. Throughout the Study Report, the terms "units" and "USP units" referred to "Ph. Eur. units." 1 Ph. Eur. unit = 0.75 USP units; therefore the doses of 500, 1000, 1500, and 2000 (Ph. Eur.) units of lipase referred to in the Study Report were equal to 375, 750, 1125, and 1500 USP units, respectively. As per the Sponsor, these changes did not affect the safety, efficacy, or overall conclusions of the study. In the tables of efficacy and safety results in Sections 6 and 7 of this review, this reviewer has modified each of the tables of efficacy and safety results provided in the 20-101 Study Report with the correct doses.

Study PNCRLP-CYS-1001

This study was a Phase 1, single-dose, open-label, randomized, 2-way crossover study of Pancreaze capsules in subjects ages 18 to 85 years who had severe exocrine pancreatic insufficiency (EPI). A total of 13 subjects were enrolled, and 12 completed the study. Subjects were randomized to 2 treatment sequences, each composed of two treatments. Treatment A consisted of a high-fat liquid meal, and treatment B consisted of 3 Pancreaze 21 capsules administered simultaneously with a high-fat liquid meal. There were 2 days of washout period in between the treatments. In each treatment, subjects were intubated with a Dreiling-like tube after overnight fast. A 30-minute washout duodenal fluid sample followed by a 30-minute baseline duodenal fluid sample was collected after a successful intubation. Subsequently, appropriate study treatment was administered orally. Duodenal fluid samples were drawn continuously for 2 hours, and pooled every 15 minutes for analytical purposes. Gastric fluid was collected at the end of each study period. After the completion of sample collection, the Dreiling-like tube was removed.

The clinical pharmacology reviewer noted that the bioavailability study using the intubation procedure is considered unreliable for assessing the *in vivo* delivery of pancreatic enzymes to the duodenum. The bioavailability study is not a required study for NDA approval. (See also Section 4.4.)

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is as follows:

Pancreaze (pancrelipase) is indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

6.1.1 Methods

Inclusion Criteria for Study 20-101

Subjects were enrolled in the study provided they satisfied the following inclusion criteria:

- Male and/or female infants/toddlers aged six to 30 months. (Prior to Protocol Amendment No. 2 dated July 18, 2005, this inclusion criterion was ‘’Male and/or Female infants/toddlers aged six to 24 months.’’)
- Diagnosis of CF confirmed by genetic testing including chromosomal analysis and/or clinical criteria including abnormal results of pilocarpine iontophoresis sweat

testing consistent with diagnosis of CF.
- Historical documentation of abnormal CFA or <15 micrograms fecal elastase/gram stool consistent with diagnosis of CF-related pancreatic insufficiency.
- Subject's parent or legal guardian must sign informed consent form.
- Stable patient requiring enzyme therapy for management of steatorrhea in patients with defined diagnosis as set forth by criteria 2 and 3 above.

Inclusion Criteria for Study PNCRLPCYS3001

Subjects had to satisfy the following criteria to be enrolled in the study:

- Male or female;
- Adults ≥18 to 60 years of age or children/adolescents 7 to <18 years of age;
- Diagnosis of cystic fibrosis confirmed by genotype analysis or sweat chloride results (>60 mmol/L);
- Require PERT to control clinical symptoms of EPI (nausea, vomiting, bloating, diarrhea, oily/greasy stools, and abdominal pain) with a history of steatorrhea;
- Documentation of an abnormal percent CFA or by a fecal elastase test (<100 μg fecal elastase/gram stool) of cystic fibrosis-related pancreatic insufficiency within 3 months before screening. If results were not available or were older than 3 months, a fecal elastase test was to be performed during the screening phase;
- Receiving a stable diet and dose of pancreatic enzyme supplementation that had provided satisfactory sign and symptom control of EPI for at least 1 month before screening for this study;
- Subjects (or their legally acceptable representatives) must have signed an informed consent document indicating that they understood the purpose of and procedures required for the study and were willing to participate in the study. Assent was also required of children capable of understanding the nature of the study (typically 7 years and older);
- Medically stable on the basis of the physical examination, medical history, and vital signs performed at screening. If there were abnormalities, they were to be consistent with the underlying illness in the study population;
- Females of childbearing potential must have had a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at the screening visit;
- Subjects of childbearing potential must have agreed not to become pregnant while participating in the study by abstaining from sexual activity or using an acceptable method of birth control. Acceptable methods of birth control included the following: an intrauterine device, hormonal contraceptives, double-barrier method, and male partner sterilization; and
- Subjects using gastrointestinal medications or medications affecting the gastrointestinal tract (other than oral pancreatic enzymes) including: acid blockers, H2 antagonists, and proton pump inhibitors, must have maintained a stable dose of these medications for at least 30 days before the screening phase and must have agreed to maintain that dose and the timing and mode of administration throughout the study. New treatment with these medications was not to be started during the study.

Exclusion Criteria for Study 20-101

Subjects were excluded from participation in the study if they fulfilled any of the following criteria:

- Stable antibiotic therapy for small bowel overgrowth or chronic pulmonary infection.
- Hypersensitivity to porcine products.
- Use of prokinetics including metoclopramide or cisapride.
- Concurrent nasogastric tube feeding for supplemental enteral nutrition.
- Concomitant steroid therapy.
- Exacerbation of chronic lung infections.
- Use of concomitant H2 blockers or proton pump inhibitors as concomitant therapy.
- Use of herbal supplements.
- Clinically significant vomiting, malnutrition, or severe dehydration.
- Severe constipation and intestinal resection.
- Uncorrected electrolyte disorders (such as hypokalemia, hypocalcemia, hypo-magnesemia).
- Known chromosome abnormality or congenital anomalies of the gastrointestinal tract, heart or liver; including gastrointestinal tract abnormalities.
- Clinically significant disease that could interfere with the adequate assessment of the study drug.
- HIV infection.
- History of drug sensitivity to any of the study medication ingredients.
- Subject in any other investigational drug study within the previous 30 days of consent.
- Are related to those persons involved directly or indirectly with the conduct and administration of this study (i.e., principal investigator, sub-investigator, study coordinators, or other study personnel, employee of McNeil, contractors of McNeil, Johnson & Johnson subsidiaries and families of each).

Exclusion Criteria for Study PNCRLPCYS3001

Subjects were not to be enrolled into the study if it were determined upon prestudy examination that they:

- Had a history of extreme cachexia (below a threshold body mass index percentile [i.e., <tenth percentile]);
- Had a severe or acute pulmonary disease unrelated to complications of cystic fibrosis;
- Had an exacerbation of pulmonary disease within the 30 days before screening;
- Used drugs known to affect blood uric acid concentrations (e.g., aspirin, diflunisal, allopurinol, probenecid, thiazide diuretics, phenylbutazone, sulfinpyrazone);
- Had known congenital anomalies of the gastrointestinal tract;
- Had a history of distal intestinal obstruction syndrome (DIOS) within the 6 months before the screening phase or requiring surgery for management;

- If using stable antibiotic therapy must have maintained a stable dose of these medications for at least 30 days before the screening phase and agreed to maintain that dose and the timing and mode of administration throughout the study. For subjects not on stable antibiotic therapy, no new intravenous inpatient treatment with these medications was to be started during the study;
- Had a hypersensitivity to porcine products or history of drug sensitivity to any of the study drug ingredients;
- Had used prokinetics, e.g., metoclopramide, cisapride, antidiarrheals (including Imodium) within 30 days of the screening phase;
- Concurrently used tube feeding for supplemental enteral nutrition;
- Had an organ transplant (e.g., heart, liver, kidney, lung);
- Were using concomitant systemic steroid therapy;
- Had clinically significant vomiting, malnutrition, or severe dehydration;
- Had severe constipation related to DIOS; or constipation requiring mineral oil or cathartic laxatives including Miralax;
- Had a significant intestinal resection;
- Had clinically significant disease that could interfere with the adequate assessment of the study drug;
- Have unstable electrolyte disorders (i.e., hypokalemia, hypocalcemia, or hypomagnesemia) or have severe liver disease, which, in the opinion of the investigator, indicated they should not participate.
- Had any condition which, in the opinion of the investigator, would compromise the well-being of the subject or the study;
- Were an employee of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, or were a family member of the employees or the investigator; or
- Had participated in any other investigational drug study within 30 days of the screening phase for this study.

6.1.2 Demographics

The inclusion and exclusion criteria for both studies differed due to the ages of subjects enrolled. Study PNCRLPCYS3001 enrolled children/adolescents 7 to <18 years of age and adults ≥18 to 60 years of age compared with Study 20-101, which enrolled infants and toddlers 6 to 30 months old. Both studies required that subjects were diagnosed with CF, and had a history of abnormal Coefficient of Fat Absorption (CFA) or a fecal elastase test with diagnosis of CF-related pancreatic insufficiency, and required pancreatic enzyme replacement therapy (PERT) to control clinical symptoms. See tables below.

Table 4. Demographic & Baseline Characteristics (All Subjects Enrolled In Study 20-101)

Characteristic	(N=18)
Gender n (%)	
Male	6 (33.3)
Female	12 (66.7)
Ethnicity n (%)	
Hispanic or Latino	0 (0.0)
Not Hispanic and not Latino	18 (100.0)
Race n (%)	
White	18 (100.0)
Black	0 (0.0)
Other	0 (0.0)
Age (Month)	
N	18
Mean (SD)	18.4 (7.9)
Median	16.6
(Min,Max)	(5.8, 29.6)
Weight (kg) at Visit 1 (Screening)	
N	18
Mean (SD)	10.0 (2.2)
Median	10.2
(Min,Max)	(6.7, 13.1)
Length (cm) at Visit 1 (Screening)	
N	18
Mean (SD)	78.6 (9.0)
Median	78.9
(Min,Max)	(63.0, 94.0)
Head Circumference (cm) at Visit 1 (Screening)	
N	18
Mean (SD)	46.1 (2.4)
Median	45.9
(Min,Max)	(41.0, 50.0)

(from page 63 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Table 5. Demographic and Baseline Characteristics (Study 20-101)

Demographic Characteristic	375 units Lipase/kg/meal N=4	750 units Lipase/kg/meal N=5	1125 units Lipase/kg/meal N=4	1500 units Lipase/kg/meal N=4	Total N=17
Gender n (%)					
Male	1 (25.0)	2 (40.0)	2 (50.0)	1 (25.0)	6 (35.3)
Female	3 (75.0)	3 (60.0)	2 (50.0)	3 (75.0)	11 (64.7)
Ethnicity n (%)					
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not Hispanic and not Latino	4 (100.0)	5 (100.0)	4 (100.0)	4 (100.0)	17 (100.0)
Race n (%)					
White	4 (100.0)	5 (100.0)	4 (100.0)	4 (100.0)	17 (100.0)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age (Month)					
n	4	5	4	4	17
Mean (SD)	24.9 (6.1)	15.7 (6.1)	13.2 (10.8)	20.8 (6.3)	18.5 (8.2)
Median	27.9	16.4	9.0	18.8	16.5
(Min,Max)	(15.8, 28.2)	(7.0, 23.2)	(5.8, 28.9)	(16.1, 29.6)	(5.8, 29.6)
Weight (kg) at Visit 1 (Screening)					
n	4	5	4	4	17
Mean (SD)	11.4 (1.7)	10.0 (2.1)	8.6 (2.8)	10.6 (2.1)	10.1 (2.2)
Median	11.8	9.8	7.6	10.7	10.6
(Min,Max)	(9.3, 12.9)	(7.5, 13.0)	(6.7, 12.6)	(7.9, 13.1)	(6.7, 13.1)
Length (cm) at Visit 1 (Screening)					
n	4	5	4	4	17
Mean (SD)	86.0 (8.5)	75.7 (7.8)	71.7 (10.0)	82.6 (5.2)	78.8 (9.2)
Median	87.9	74.2	68.9	81.8	80.5
(Min,Max)	(74.0, 94.0)	(65.0, 85.0)	(63.0, 86.0)	(77.2, 89.5)	(63.0, 94.0)
Head Circumference (cm) at Visit 1 (Screening)					
n	4	5	4	4	17
Mean (SD)	48.0 (2.5)	45.7 (0.6)	44.1 (3.3)	46.9 (2.1)	46.1 (2.5)
Median	48.9	45.7	43.3	46.0	45.7
(Min,Max)	(44.3, 50.0)	(44.8, 46.5)	(41.0, 48.8)	(45.5, 50.0)	(41.0, 50.0)

(modified from pages 65 & 66 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Overall, the majority of the subjects in Study PNCRLPCYS3001 were male (55%), ≥18 years old (65%), and White (90%), as detailed in the table below. There were 14 children/adolescent subjects (35%) and 26 adult subjects (65%) enrolled in the study, with a similar distribution of subjects in these age categories between treatment groups. Mean (SD) percent CFA at baseline was 89.4% (4.88%) overall, and no notable differences in percent CFA between treatment groups. In the placebo group, 65% of the subjects were males and 35% were females.

Among subjects 7 to <18 years old, the mean age was slightly higher in the placebo group (13.5 years, range 8.9 to 17.4 years) compared with the Pancreaze group (11.3 years, range 8.7 to 13.3 years) and subjects were slightly heavier in the placebo group (46.7 kg, range 27.0 to 73.8 kg) compared with the Pancreaze group (41.4 kg, range 26.1 to 59.2 kg). Among subjects ≥18 to 60 years old, subjects in the placebo group were heavier (68.2 kg, range 49.0 to 91.0 kg) compared with the Pancreaze group (62.3 kg, range 45.7 to 82.1 kg).

Table 6. Summary of Demographic and Baseline Characteristics (PNCRLPCYS3001)

Category Statistics	PLACEBO (N=20)	PANCREASE MT (N=20)	TOTAL (N=40)
Age – All Subjects			
N	20	20	40
Mean (SD)	23.4 (11.58)	24.0 (13.44)	23.7 (12.39)
Median	20.4	21.3	21.3
Range	8.9-47.5	8.7-57.1	8.7-57.1
Age Category			
< 7 years old	0	0	0
7 - <18 years old	8(40%)	6(30%)	14(35%)
>= 18 - 60 years old	12(60%)	14(70%)	26(65%)
> 60 years old	0	0	0
7 - <18 years old			
N	8	6	14
Mean (SD)	13.5 (3.54)	11.3 (1.66)	12.6 (3.00)
Median	13.9	11.5	12.1
Range	8.9-17.4	8.7-13.3	8.7-17.4
>= 18 - 60 years old			
N	12	14	26
Mean (SD)	30.1 (10.16)	29.4 (12.57)	29.7 (11.30)
Median	26.6	24.0	24.9
Range	18.1-47.5	18.0-57.1	18.0-57.1
Sex - N(%)			
Male	13(65%)	9(45%)	22(55%)
Female	7(35%)	11(55%)	18(45%)
Race - N(%)[a]			
White	19(95%)	17(85%)	36(90%)
Black or African American	1(5%)	1(5%)	2(5%)
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	1(5%)	1(3%)
Other (Including Missing Or Unknown)	0	1(5%)	1(3%)
Ethnicity - N(%)			
Not Hispanic or Latino	19(95%)	19(95%)	38(95%)
Hispanic or Latino	1(5%)	1(5%)	2(5%)
Height - cm			
N	20	20	40
Mean (SD)	165.7 (15.38)	161.6 (15.69)	163.6 (15.48)
Median	167.4	163.5	165.7
Range	131.9-184.0	129.0-189.5	129.0-189.5
Height - cm: 7 - <18 years old			
N	8	6	14
Mean (SD)	153.5 (16.51)	142.9 (10.09)	148.9 (14.67)
Median	153.9	144.1	147.1
Range	131.9-179.2	129.0-158.0	129.0-179.2

[a] If a subject reported more than one race, then this subject was included as Other.

(from page 38 & 39 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Table 6 (cont.). Demographic and Baseline Characteristics (PNCRLPCYS3001)

Category Statistics	PLACEBO (N=20)	PANCREASE MT (N=20)	TOTAL (N=40)
Height - cm: >= 18 - 60 years old			
N	12	14	26
Mean (SD)	173.9 (7.34)	169.6 (9.56)	171.5 (8.72)
Median	174.5	169.3	171.3
Range	162.5-184.0	155.0-189.5	155.0-189.5
Weight - kg			
N	20	20	40
Mean (SD)	59.6 (17.05)	56.0 (15.16)	57.8 (16.03)
Median	59.7	55.2	58.0
Range	27.0-91.0	26.1-82.1	26.1-91.0
Weight - kg: 7 - <18 years old			
N	8	6	14
Mean (SD)	46.7 (16.07)	41.4 (12.35)	44.4 (14.33)
Median	45.0	44.6	44.6
Range	27.0-73.8	26.1-59.2	26.1-73.8
Weight - kg: >= 18 - 60 years old			
N	12	14	26
Mean (SD)	68.2 (11.65)	62.3 (11.66)	65.0 (11.81)
Median	67.8	62.1	65.5
Range	49.0-91.0	45.7-82.1	45.7-91.0
COA-Fat (%)[b]			
N	20	20	40
Mean (SD)	90.5 (4.51)	88.2 (5.07)	89.4 (4.88)
Median	90.7	88.9	90.2
Range	79.4-98.6	78.1-94.9	78.1-98.6

Key: COA = coefficient of absorption; SD = standard deviation
[a] If a subject reported more than one race, then this subject was included as Other.
[b] Baseline percent COA-fat is the last measurement before the first dose in the open-label phase for percent COA-fat.

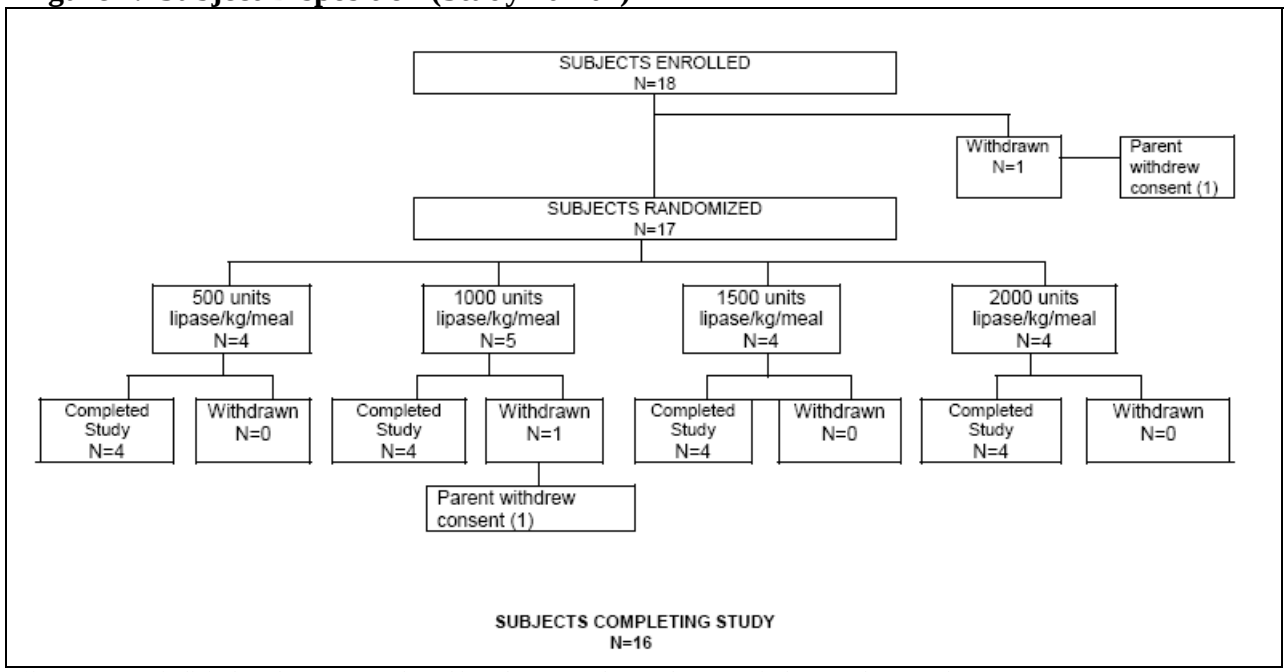
(from pages 38 and 39 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

6.1.3 Subject Disposition

Study 20-101

Data were available for 18 enrolled subjects. Overall, 17 subjects were randomized to pancrelipase microtablets at 375 units lipase/kg/meal, 750 units lipase/kg/meal, 1125 units lipase/kg/meal, or 1500 units lipase/kg/meal. Sixteen subjects completed the study. The figure below summarizes the status of the subjects in Study 20-101.

Figure 2. Subject Disposition (Study 20-101)



(from page 57 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Study PNCRLPCYS3001

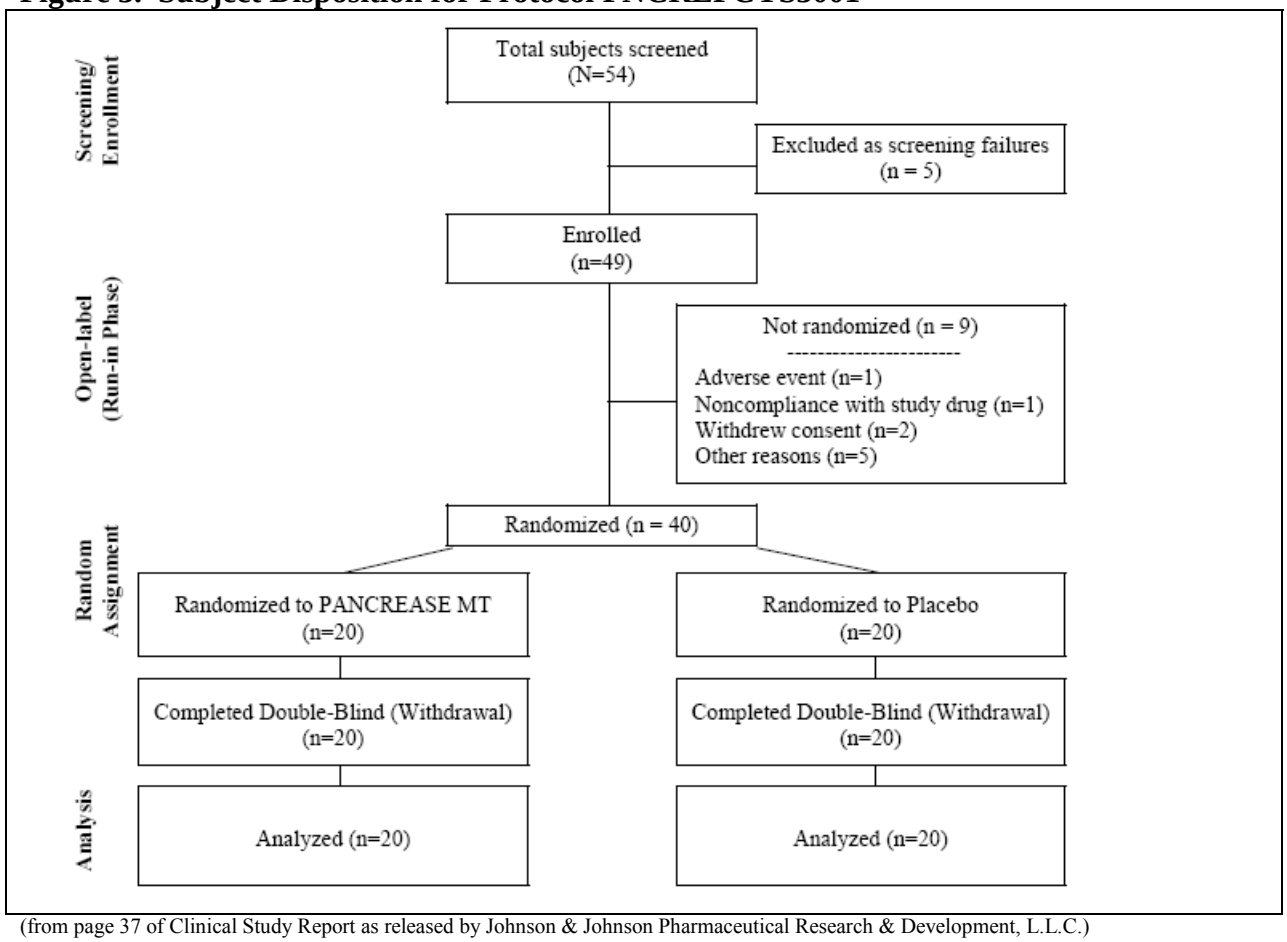
Fifty-four subjects were screened for entry into the study, and 5 of these subjects failed screening procedures. The remaining 49 subjects were enrolled; 1 subject withdrew consent and was discontinued from the study prior to receiving open-label study drug. The remaining 48 subjects entered the Run-in Phase of the study and received open-label study drug (see table and figure below).

Table 7. Subject Disposition Summary (All Enrolled Subjects in Study PNCRLPCYS3001)

	PANCREASE MT	Placebo	Not randomized	Total
Number of subjects enrolled	20	20	9	49
Number of subjects randomized	20	20	0	40
Number of subjects entered the study				
Number of subjects entered run-in	20	20	8	48
Number of subjects entered double-blind	20	20	0	40
Number of subjects included in ITT population	20	20	0	40
Number of subjects included in per-protocol population	20	19	0	39
Number of subjects included in completers population	20	20	0	40
Number of subjects completed the study	20	20	0	40

(from page 36 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Figure 3. Subject Disposition for Protocol PNCRLPCYS3001



(from page 37 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Eight of these subjects discontinued during the open-label phase and were excluded from the randomization; the remaining 40 subjects were randomized in a 1:1 fashion to receive either Pancreaze or placebo. All 40 subjects completed the study. The 9 enrolled subjects who discontinued from the study prior to randomization discontinued for the following reasons: 2 subjects withdrew consent (1 prior to receiving open-label study drug); adverse event (1 subject); noncompliance with study drug (1 subject); and "other reasons" (5 subjects); these 5 subjects had percent CFA values that were ≤80% (48%. 59.8%, 64.2%, and 77.1%) or were not obtained and therefore did not meet randomization criteria.

6.1.4 Primary Efficacy Endpoints

The primary efficacy measure in each individual study and in the pooled analysis was the change in coefficient of fat absorption (CFA).

Study PNCRLPCYS3001

In Study PNCRLPCYS3001, this parameter was calculated from the 72-hour stool collection phase at the end of the open-label phase to the 72-hour stool collection phase at the end of the randomized, double-blind withdrawal phase.

The primary endpoint of the study, change in the coefficient of fat absorption (percent CFA) from the 72-hour inpatient period in the open-label phase to the 72-hour period inpatient period in the double-blind (withdrawal) phase, is presented in the table and figure below. At the end of the double-blind phase, subjects in the Pancreaze group had a 1.4% decrease in mean percent CFA, compared with subjects in the placebo group, who had a 34.1% decrease in mean percent CFA. Based on the ANCOVA model with treatment as a factor and baseline percent CFA as a covariate, this difference was statistically significant, favoring Pancreaze ($p < 0.001$).

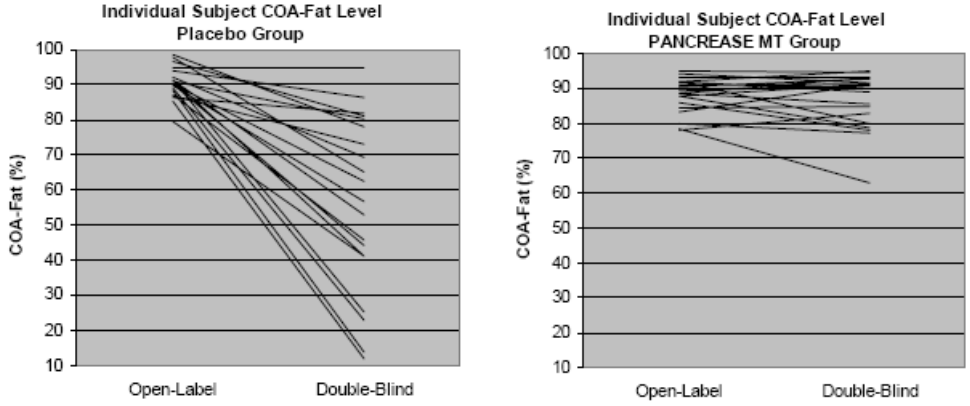
Table 8. Summary of Change in CFA (%) (ITT Analysis Set in Study PNCRLPCYS3001)

Timepoint Statistics	PLACEBO (N=20)	PANCREASE MT (N=20)	TOTAL (N=40)
Baseline[a]			
N	20	20	40
Mean (SD)	90.5(4.51)	88.2(5.07)	89.4(4.88)
Median	90.7	88.9	90.2
Range	79-99	78-95	78-99
End of double blind[a]			
N	20	20	40
Mean (SD)	56.4(24.93)	86.8(8.09)	71.6(23.91)
Median	59.5	90.7	80.0
Range	12-95	63-95	12-95
Change from baseline[a]			
N	20	20	40
Mean (SD)	-34.1(23.03)	-1.5(5.88)	-17.8(23.44)
Median	-32.9	-0.0	-8.5
Range	-75- 0	-16- 8	-75- 8
P-Value[b]		<0.001	

[a] Include subjects who had data at the 2 time points. Baseline was measured at Visit 2 (open-label) and end of double-blind was measured at Visit 3.
[b] The p-value is from ANCOVA model with treatment as a factor and baseline percent COA-fat as a covariate.

(from page 45 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Figure 4. Individual Subject Percent CFA Level From End of Open-label Phase to End of Double-Blind Phase (ITT Analysis Set in Study PNCRLPCYS3001)



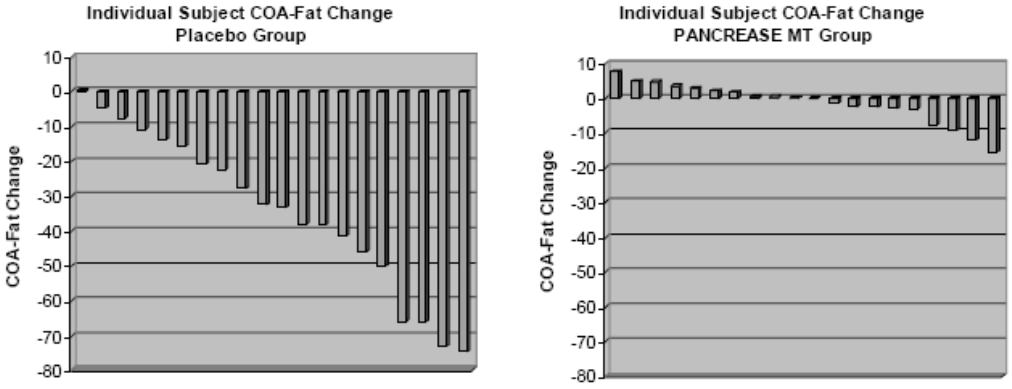
(from page 46 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Subjects had to have achieved a level of 80% or more percent CFA at the end of the open-label treatment phase in order to be randomized. For subjects in the Pancreaze group (i.e., subjects who were continuously treated with their stabilized Pancreaze doses), all but 1 subject maintained their percent CFA level at or above about 80% at the end of the double-blind phase. Even in that one subject in the Pancreaze group, the percent CFA level at the end of the double-blind phase was above 60% as compared to the 10 subjects in the placebo group whose percent CFA level at the end of the double-blind phase fell below the 60% level. Additionally, it is of note that this subject in the Pancreaze group had the lowest percent CFA level at the end of the open-label phase amongst all the subjects in both the placebo and Pancreaze groups. This subject may have been the most severely affected at the end of the open-label phase, and given that this subject's percent CFA level at the end of the double-blind phase dropped by only about 15% as compared to the drops of 40% or more in at least 10 subjects in the placebo group, the Pancreaze treatment may have been significant and beneficial to the patient.

For subjects in the placebo group (i.e., subjects whose open-label Pancreaze treatment was discontinued for the duration of the double-blind phase), varying degrees of decrease were seen in percent CFA level by the end of the double-blind phase. The change from baseline result for Pancreaze subjects has small variability and a smaller standard deviation compared with subjects in the placebo group.

The amount of change in percent CFA from the end of the open-label phase to the end of the double-blind withdrawal phase is illustrated for individual subjects in the figure below. Subjects receiving placebo showed a greater change in percent CFA level (range 0 to -75%) compared with subjects receiving Pancreaze (range 8 to –16%).

Figure 5. Individual Subject Change in Percent CFA Level From End of Open-Label Phase to End of Double-Blind Phase (ITT Analysis Set in Study PNCRLPCYS3001)



(from page 46 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

The change in percent CFA analysis was also performed for the 2 age subgroups (adults ≥18 to 60 years old and children/adolescents 7 to <18 years old) as noted in the table below. Consistent treatment effects were seen across the age subgroups. For subjects who were continuously treated with Pancreaze, the mean percent change of CFA levels in both the adult and children/adolescent subgroups were small through the end of the double-blind period (mean change of -1.2% in adults and -2.0% in the children/adolescents). However, in the placebo group, both the adult and children/adolescent subgroups showed a significant decrease in the mean percent CFA (mean of -38.2% in adults and -28.1% in the children/adolescents) from the end of the open-label phase.

Table 9. Summary of Change in Percent CFA by Age Group (ITT Analysis Set in Study PNCRLPCYS3001)

	Adults (18 to 60 years old)		Children/Adolescents (7 to <18 years old)	
Timepoint Statistics	Placebo (N=12)	PANCREASE MT (N=14)	Placebo (N=8)	PANCREASE MT (N=6)
End of open-label phase				
N	12	14	8	6
Mean (SD)	89.7 (4.46)	87.8 (5.44)	91.7 (4.60)	89.1 (4.42)
Median (Range)	90.2 (79;98)	89.0 (78;95)	91.5 (85;99)	90.3 (84;94)
End of double-blind withdrawal phase				
N	12	14	8	6
Mean (SD)	51.5 (25.47)	86.6 (9.38)	63.6 (23.81)	87.1 (4.46)
Median (Range)	44.9 (14;95)	91.2 (63;95)	71.2 (12;86)	87.3 (80;92)
Change from end of open-label to end of double-blind phase				
N	12	14	8	6
Mean (SD)	-38.2 (24.42)	-1.2 (5.87)	-28.1 (20.78)	-2.0 (6.40)
Median (Range)	-39.9 (-75;0)	0.2 (-16;5)	-21.7 (-73;-8)	-2.7 (-12;8)

(from page 47 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

The table below represents the summary change in percent CFA by gender.

Table 10. Change in Percent CFA by Gender (PNCRLPCYS3001)

Treatment / Statistics	Placebo		Pancreaze	
	Male (N=13)	Female (N=7)	Male (N=9)	Female (N=11)
Mean (SD)	-43.2 (22.3)	-17.3 (13.2)	-1.9 (6.7)	-1.1 (5.4)
Median (Range)	-41.4 (-74.6, -7.6)	-15.6 (-38.3, 0.3)	0.6 (-15.6, 4.8)	-0.15 (-12.1, 7.6)

(Table above generated by clinical reviewers using datasets provided by sponsor in the submission.)

In both genders, patients in the Pancreaze group showed little change in the percent CFA (-1.9% change in males; -1.1% change in females) as opposed to the placebo group where there were significant changes in the percent CFA in both genders (-41.4% change in males; -15.6% change in females).

From the above data pertaining to age and gender, it can be concluded that no substantial differences in mean change in CFA are present with respect to age and gender.

Study 20-101

In Study 20-101, a primary efficacy endpoint was the change in CFA measured from the Visit 2 (Randomization) to Visit 3 (End of Study). Two additional primary efficacy endpoints were daily palatability of study medication and noninvasive measurement of carbon dioxide (CO_2) expired using a $^{13}CO2$ mixed triglyceride (MTG) breath test.

Daily palatability was assessed using a 4-point scale (0 = poor, 1 = fair, 2 = good, 3 = excellent) daily, which was treated as a continuous value. Three sets of analyses on palatability data were conducted for the open-label run-in phase and randomized phase separately. All subjects enrolled were included in the analysis for the open-label run-in phase. All randomized subjects were included in the analysis for the randomized phase.

The percentage of CO_2 expired (cumulative % ^{13}C) by a MTG breath test was measured; the applicant proposed this as a surrogate marker of lipase activity and pharmacodynamic effect of pancreatic enzyme therapy. A $^{13}CO2$ MTG breath test was performed on each subject after ingesting a liquid or solid test meal containing $^{13}CO_2$ MTG. Breath samples were collected every 15 minutes for 6 hours. The percentage of exhaled $^{13}CO2$ MTG was measured using infrared mass spectrometry and the cumulative expired $^{13}CO_2$ was calculated.

The table below presents the summary of CFA by treatment group for all randomized subjects who completed the study.

Table 11. Summary of Coefficient of Fat Absorption (CFA – All Randomized Subjects Who Completed the Study

CFA (%)	375 units Lipase/kg/meal (N=4)	750 units Lipase/kg/meal (N=4)	1125 units Lipase/kg/meal (N=4)	1500 units Lipase/kg/meal (N=4)
Visit 2 (Day 6: Randomization)				
n	4	4	4	4
Mean(SD)	93.33(2.438)	89.99(5.102)	81.40(10.835)	92.63(2.601)
Median	92.95	89.85	82.83	92.21
(Min, Max)	(91.0, 96.4)	(85.0, 95.3)	(67.1, 92.8)	(90.3, 95.8)
Visit 3(Day 11: End of Study)				
n	4	4	4	4
Mean(SD)	91.59(3.303)	91.13(3.949)	80.24(12.670)	90.49(1.855)
Median	92.71	90.74	82.94	90.06
(Min, Max)	(86.8, 94.2)	(86.8, 96.3)	(63.3, 91.8)	(88.9, 92.9)
Change[a] from Visit 2				
n	4	4	4	4
Mean(SD)	-1.74(2.529438)	1.14(2.802)	-1.16(2.584)	-2.14(3.227)
Median	-1.75	0.73	-1.56	-1.29
(Min, Max)	(-4.3, 0.8)	(-1.8, 4.9)	(-3.8, 2.3)	(-6.7, 0.7)

CFA (%) = [Fat Intake (grams) – Fat Excretion (grams)] x 100/Fat Intake (grams)
a: Value at Visit 3 – Value at Visit 2

At the time of randomization, mean CFA was 93.3%, 90.0%, 81.4%, and 92.6% in the 375 units lipase/kg/meal, 750 units lipase/kg/meal, 1125 units lipase/kg/meal, and 1500 units lipase/kg/meal groups, respectively. There were no clinically important changes in the mean CFA from randomization to the end of study within any treatment group. In addition, there were no clinically important differences among treatment groups in the mean change in CFA from randomization to the end of study. The mean changes in CFA were -1.74%, 1.14%, -1.16%, and -2.14% in the 375 units lipase/kg/meal, 750 units lipase/kg/meal, 1125 units lipase/kg/meal, and 1500 units lipase/kg/meal groups, respectively.

The table below shows a summary of daily global assessment of palatability by treatment group for all randomized subjects who completed the study.

Table 12. Global Assessment (Daily) of Palatability*

Palatability	Open-label Run-in Period 375 units/lipase/kg/meal (n=16)	Double Blind Randomized Period 375 units Lipase/kg/meal N=4	750 units Lipase/kg/meal N=4	1125 units Lipase/kg/meal N=4	1500 units Lipase/kg/meal N=4	Total N=16
Overall						
n	16	4	4	4	4	16
Mean (SD)	2.2 (1.07)	2.8 (0.50)	2.0 (1.13)	2.0 (0.82)	1.6 (1.60)	2.1 (1.06)
Median	2.8	3.0	2.0	2.1	1.8	2.6
(Min,Max)	(0.0, 3.0)	(2.0, 3.0)	(1.0, 3.0)	(1.0, 3.0)	(0.0, 3.0)	(0.0, 3.0)
Maximum						
n	16	4	4	4	4	16
Mean (SD)	2.3 (1.00)	2.8 (0.50)	2.1 (1.03)	2.3 (0.96)	1.8 (1.50)	2.2 (1.02)
Median	3.0	3.0	2.3	2.5	2.0	3.0
(Min,Max)	(0.0, 3.0)	(2.0, 3.0)	(1.0, 3.0)	(1.0, 3.0)	(0.0, 3.0)	(0.0, 3.0)
Minimum						
n	16	4	4	4	4	16
Mean (SD)	2.1 (1.06)	2.8 (0.50)	2.0 (1.15)	2.0 (0.82)	1.5 (1.73)	2.1 (1.12)
Median	2.0	3.0	2.0	2.0	1.5	2.5
(Min,Max)	(0.0, 3.0)	(2.0, 3.0)	(1.0, 3.0)	(1.0, 3.0)	(0.0, 3.0)	(0.0, 3.0)

Palatability Scores: 0 = poor; 1 = fair; 2 = good; 3 = excellent.

*All Randomized Subjects Who Completed the Study
(modified from page 75 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

In the open-label-run-in period, the overall mean palatability score was 2.2. In the randomized period, the total overall mean palatability score was 2.1. In the individual randomized treatment groups, scores were ≥2.0 in all but the highest dosage group; overall mean palatability scores were 2.8, 2.0, 2.0, and 1.6 for the 375 units lipase/kg/meal, 750 units lipase/kg/meal, 1125 units lipase/kg/meal, and 1500 units lipase/kg/meal groups, respectively. The mean minimum and maximum scores were similar to the mean overall scores. A clinically meaningful change in the palatability score used by the sponsor has not been established, so the clinical relevance of these results is not known.

The table below presents the summary of cumulative % ^{13}C from the breath test by treatment group for all randomized subjects who completed the study.

Table 13. Summary of Cumulative % ^{13}C (from Breath Test) – All Randomized Subjects Who Completed the Study

Cumulative % ^{13}C	375 units Lipase/kg/meal N=4	750 units Lipase/kg/meal N=5	1125 units Lipase/kg/meal N=4	1500 units Lipase/kg/meal N=4
Visit 2 (Day 6: Randomization)				
n	4	4	4	4
Mean (SD)	17.34 (5.960)	0.72 (12.372)	19.05 (26.929)	9.67 (17.257)
Median	17.60	0.77	7.17	1.42
(Min,Max)	(10.4, 23.7)	(-11.4, 12.7)	(2.7, 59.2)	(0.3, 35.5)
Visit 3 (Day 11: End of Study)				
n	3	4	4	4
Mean (SD)	18.68 (4.500)	7.87 (9.157)	11.65 (11.197)	13.80 (23.415)
Median	18.66	7.48	9.64	2.71
(Min,Max)	(14.2, 23.2)	(-0.9, 17.4)	(0.2, 27.1)	(0.9, 48.9)
Change[a] from Visit 2				
n	3	4	4	4
Mean (SD)	-0.95 (5.279)	7.15 (4.585)	-7.41 (16.763)	4.14 (6.167)
Median	-0.51	7.49	-1.14	1.29
(Min,Max)	(-6.4, 4.1)	(1.2, 12.4)	(-32.2, 4.8)	(0.6, 13.4)

a: Value at Visit 3 - Value at Visit 2

(modified from page 78 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

There were some differences between treatment groups with respect to change from Visit 2 in cumulative % ^{13}C, with mean cumulative % ^{13}C increasing from Visit 2 to Visit 3 in the 1000 units lipase/kg/meal and 2000 units lipase/kg/meal groups (7.15%, 4.14%, respectively) and decreasing in the 500 units lipase/kg/meal and 1500 units lipase/kg/meal groups (–0.95%, -7.41%, respectively). A clinically meaningful change in the MTG breath test used by the sponsor has not been established, so the clinical relevance of these results is not known.

6.1.5 Secondary Efficacy Endpoints

The key secondary efficacy endpoint in each individual study and in the pooled studies was CNA. Nitrogen was measured in the stool collection as the surrogate for protein excretion.

Study PNCRLPCYS3001

In Study PNCRLPCYS3001 the change in CNA was measured from the 72-hour open-label phase stool collection period to the end of the 72-hour stool collection of the double-blind withdrawal phase.

The change in the coefficient of protein (nitrogen) absorption (percent CNA) from the 72-hour inpatient period in the open-label phase to the 72-hour period inpatient period in the double-blind

(withdrawal) phase, is presented in the table below. Nitrogen was quantitated in the 72-hour stool collection as the surrogate of protein excretion. At the end of the double-blind phase, subjects in the Pancreaze group had a 1.3% increase in mean percent coefficient of protein (nitrogen) absorption (CNA), compared with subjects in the placebo group, who had a 26.5% decrease in mean percent CNA. Based on the ANCOVA model with treatment as a factor and baseline percent CNA as a covariate, this difference was statistically significant, favoring Pancreaze ($p < 0.001$). 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.

Table 14. Summary of Change in Percent CNA (%) (ITT Analysis Set in Study PNCRLPCYS3001)

Timepoint Statistics	PLACEBO (N=20)	PANCREASE MT (N=20)	TOTAL (N=40)
Baseline[a]			
N	20	20	40
Mean (SD)	84.5(7.78)	81.2(6.42)	82.8(7.24)
Median	84.4	81.7	82.3
Range	66- 98	64- 93	64- 98
End of double blind[a]			
N	20	20	40
Mean (SD)	57.9(19.73)	82.4(6.00)	70.2(19.00)
Median	58.3	82.8	78.4
Range	20- 84	68- 94	20- 94
Change from baseline[a]			
N	20	20	40
Mean (SD)	-26.5(15.30)	1.3(4.71)	-12.6(17.97)
Median	-24.3	1.2	-5.2
Range	-62- -3	-7- 9	-62- 9
P-Value[b]		<0.001	

[a] Includes subjects who had data at the 2 time points. Baseline was measured at Visit 2 (open-label) and end of double-blind was measured at Visit 3.
[b] The p-value is from ANCOVA model with treatment as a factor and baseline percent COA-protein (nitrogen) as a covariate.

(from page 48 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

An additional key secondary efficacy endpoint of Study PNCRLPCYS3001 was the effect of Pancreaze on improvement in clinical signs and symptoms of EPI in adults and children/adolescents with CF and clinical symptoms of EPI, i.e., nausea, vomiting, bloating, diarrhea, greasy stools, and abdominal pain. The relevance of these findings in a short-term study is not known and these endpoints were not felt to be supportive of labeling.

Study 20-101

In Study 20-101, a secondary efficacy endpoint was the Clinical Global Impression of Severity of Illness Subscale (CGI-S). The table below shows a summary of CGI-S scores by treatment group for all randomized subjects who completed the study.

Table 15. Clinical Global Impression of Severity of Illness Subscale (CGI-S)*

CGI-S	375 units Lipase/kg/meal N=4	750 units Lipase/kg/meal N=4	1125 units Lipase/kg/meal N=4	1500 units Lipase/kg/meal N=4
Visit 1 (Day 1: Screening)				
n	4	4	4	4
Mean (SD)	1.3 (0.50)	1.5 (0.58)	1.3 (0.50)	1.8 (1.50)
Median	1.0	1.5	1.0	1.0
(Min,Max)	(1.0, 2.0)	(1.0, 2.0)	(1.0, 2.0)	(1.0, 4.0)
Visit 2 (Day 6: Randomization)				
n	4	4	4	4
Mean (SD)	1.3 (0.50)	1.5 (0.58)	1.3 (0.50)	1.3 (0.50)
Median	1.0	1.5	1.0	1.0
(Min,Max)	(1.0, 2.0)	(1.0, 2.0)	(1.0, 2.0)	(1.0, 2.0)
Visit 3 (Day 11: End of Study)				
n	4	4	4	4
Mean (SD)	1.5 (0.58)	1.5 (0.58)	1.3 (0.50)	1.5 (0.58)
Median	1.5	1.5	1.0	1.5
(Min,Max)	(1.0, 2.0)	(1.0, 2.0)	(1.0, 2.0)	(1.0, 2.0)
Change[a] from Visit 2 to Visit 3				
n	4	4	4	4
Mean (SD)	0.3 (0.50)	0.0 (0.00)	0.0 (0.00)	0.3 (0.50)
Median	0.0	0.0	0.0	0.0
(Min,Max)	(0.0, 1.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 1.0)

CGI-S Scores: 1 = Normal, not at all ill; 2 = Borderline ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; 7 = Among the most extremely ill patients.
a: Value at Visit 3 - Value at Visit 2

*All Randomized Subjects Who Completed the Study
(modified from pages 79 & 80 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

At the time of screening, mean CGI-S scores were 1.3, 1.5, 1.3, and 1.8 in the 375 units lipase/kg/meal, 750 units lipase/kg/meal, 1125 units lipase/kg/meal, and 1500 units lipase/kg/meal groups, respectively. There were no clinically significant changes from randomization to the end of study in mean CGI-S scores within any treatment group. Additionally, there were no clinically significant differences among treatment groups in the change in mean CGI-S scores from randomization to the end of study. The changes in mean CGI-S scores from randomization were 0.3, 0.0, 0.0, and 0.3 in the 375 units lipase/kg/meal, 750 units lipase/kg/meal, 1125 units lipase/kg/meal, and 1500 units lipase/kg/meal groups, respectively. A clinically meaningful change in the CGI-S scores used by the sponsor has not been established, so the clinical relevance of these results is not known.

6.1.6 Other Endpoints

In Study PNCRLPCYS3001, other secondary endpoints included stool diary, clinical global impression-severity (CGI-S), clinical global impression-change (CGI-C), global assessment of change (GAC), food intake, and change in body weight. The relevance of these findings in a short-term study is unknown and these endpoints were not felt to be supportive of labeling.

In Study 20-101 other secondary endpoints included investigator assessment of improvement and parental assessment of improvement (using CGI-C), weight gain/loss during study phase, global assessment of effectiveness (GAE), mean daily calories and fat intake as measured by 24-hour food records during run-in and randomized treatment phases. The relevance of these findings in a short-term study is unknown and these endpoints were not felt to be supportive of labeling.

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

6.1.7 Subpopulations

Subgroup analyses by gender were performed by this Reviewer, and were found not to have affected the efficacy results in Study PNCRLPCYS3001 (please refer to Table 10).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All patients in the Pancreaze 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 Pancreaze was determined on an individual basis, and doses for patients were titrated to control the symptoms of EPI while remaining within CFF guidelines.

Although Pancreaze microtablets were mixed with infant formula in Study 20-101, the label for Pancreaze specifically recommends that the contents of the capsules for Pancreaze should not be mixed directly into formula or breast milk as this may diminish efficacy. (For a full discussion of an in-vitro study with Pancreaze and infant formula, please refer to the clinical pharmacology review by Dr. Lanyan Fang, Clinical Pharmacologist.)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Given that the clinical data obtained were from short-term studies, the persistence of efficacy and/or tolerance effects was not assessed in the Pancreaze clinical development program. According to the literature, the development of tolerance to PEPs does not occur and patients remain on these medications life-long.

6.1.10 Additional Efficacy Issues/Analyses

Four dosage strength formulations of Pancreaze were MT 4.2, MT 10.5, MT 16.8, and MT 21 capsules, with each containing 4,200, 10,500, 16,800, and 21,000 USP units (U) of lipase, respectively. The ratios of lipase:amylase and lipase:protease were the same in the first 3 dosage

strength formulations (MT 4.2, MT 10.5, MT and 16.8 MT), however, the ratios of lipase:amylase and lipase to protease were higher in MT 21 as compared to the three lower strength formulations. Two dosage strength formulations of Pancreaze (MT 10.5 and MT 21) were used in the pivotal study (PNCRLYPS3001). The baseline CFA, the end of treatment of CFA, and the change in CFA were summarized in both groups that received the MT 10.5 capsule and the MT 21 capsule. The results suggested that the response was similar in both capsules (Please refer to the figures and tables below).

Table 16. Summary of Change in CFA by MT 10.5 and MT 21

Timepoint Statistics	**Placebo** (N=20)	**Pancrease MT 10.5** (N=7)	**Pancrease MT 21** (N=13)
Baseline			
Mean (SD)	90.5 (4.5)	87.7 (5.2)	88.5 (5.2)
Median	90.7	88.5	89.4
Range	79.4 to 98.6	78.1 to 92.1	78.3 to 94.9
End of double blind			
Mean (SD)	56.37 (24.9)	86.5 (5.8)	86.9 (9.3)
Median	59.5	89.0	91.3
Range	12.0 to 94.8	78.7 to 93.3	62.8 to 95.0
Change from baseline			
Mean (SD)	-34.1 (23.0)	-1.2 (7.5)	-1.6 (5.1)
Median	-32.9	-1.4	0.1
Range	-74.6 to 0.3	-12.1 to 7.7	-15.6 to 3.4

(Table above generated by clinical reviewers using datasets provided by the sponsor.)

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed from the three clinical studies performed in the Pancreaze clinical development program (PNCRLPCYS3001, 20-101, and PNCRLP-CYS-1001). All three studies have been described in section 5.3 (above). Study PNCRLPCYS3001 evaluated the safety and efficacy in subjects with CF-related pancreatic insufficiency, and Study 20-101 was a supportive study for safety and efficacy.

Clinical pharmacology study PNCRLP-CYS-1001 evaluated the intraduodenal enzyme delivery of Pancreaze in subjects with severe exocrine pancreatic insufficiency. In addition, three in vitro clinical pharmacology or biopharmaceutics studies were submitted including two studies assessing the stability of enteric-coated microtablets in infant formula and baby foods (please refer to the clinical pharmacology review by Dr. Lanyan Fang, clinical pharmacologist).

The safety data from Studies PNCRLPCYS3001 and 20-101were reviewed in their entirety in this review.

7.1.2 Categorization of Adverse Events

The Sponsor adequately categorized the adverse events using MedDRA classification.

7.1.3 Pooling Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of safety data for this review was performed. Results of each study were analyzed separately.

7.2 Adequacy of Safety Assessments

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

Fifty-seven subjects were included in the Safety Analysis Set for the 2 studies (PNCRLPCYS3001 and 20-101) including 20 subjects who were administered placebo (during the double-blind phase of Study PNCRLPCYS3001) and 37 subjects in both studies who were administered Pancrease MT (Pancreaze) (see table below). Subjects administered Pancreaze spent a mean of 24.7 days in the study (range 8 to 93 days), while subjects administered placebo spent a mean of 30.4 days in the study (range 21 to 49 days). The total number of days in the study was calculated from the date of the signing of the Informed Consent to the end-of-study visit. A single subject in the Pancreaze group had a 2-month delay between the signing of the Informed Consent and randomization, resulting in a 93-day study duration.

Table 17. Total Days in Study by Treatment Group (Safety Analysis Set for Studies PNCRLPCYS3001 and 20-101)

		PANCREASE MT (lipase units/kg/day)			
Total Days in Study Statistics	Placebo (N=20)	<10,000 (N=36)	>=10,000 (N=1)	Total (N=37)	Total (N=57)
N	20	36	1	37	57
Mean (SD)	30.4 (6.90)	24.8 (16.13)	24.0	24.7 (15.90)	26.7 (13.64)
Median	28	28	24	27	27
Range	21 - 49	8 - 93	24 - 24	8 - 93	8 - 93

(from page 21 of the Integrated Summary of Safety as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Thirty-one children/adolescents (<18 years old) were included in the Safety Analysis Set for these 2 studies, including 4 subjects 0 to 1 year old, 13 subjects >1 to 5 years old, 3 subjects >5

to 10 years old, and 11 subjects >10 to <18 years old (noted in the table below). Eight children/adolescents were administered placebo (during the double-blind phase of Study PNCRLPCYS3001) and 23 children/adolescents in both studies were administered Pancreaze. The 4 subjects 0 to 1 year old spent a mean of 12.5 days in the study (range 11 to 13 days) and the 13 subjects >1 to 5 years old spent a mean of 11.9 days in the study (range 8 to 15 days). The 3 subjects >5 to 10 years old spent a mean of 29.7 days in the study (range 24 to 39 days) and the 11 subjects >10 to <18 years old spent a mean of 28.1 days in the study (range 21 to 39 days).

Table 18. Total Days in Study by Age Category and Treatment Group (Safety Analysis Set for Studies PNCRLPCYS3001 and 20-101)

AGE GROUP		PANCREASE MT (lipase units/kg/day)			
Total Days in Study Statistics	Placebo (N=8)	<10,000 (N=22)	>=10,000 (N=1)	Total (N=23)	Total (N=31)
PEDIATRIC AGE GROUP:0 - 1 year old					
n	0	4	0	4	4
Mean (SD)		12.5 (1.00)		12.5 (1.00)	12.5 (1.00)
Median		13		13	13
Range		11 - 13		11 - 13	11 - 13
PEDIATRIC AGE GROUP:>1 - 5 years old					
n	0	13	0	13	13
Mean (SD)		11.9 (1.71)		11.9 (1.71)	11.9 (1.71)
Median		12		12	12
Range		8 - 15		8 - 15	8 - 15
PEDIATRIC AGE GROUP:>5 - 10 years old					
n	2	1	0	1	3
Mean (SD)	25.0 (1.41)	39.0		39.0	29.7 (8.14)
Median	25	39		39	26
Range	24 - 26	39 - 39		39 - 39	24 - 39
PEDIATRIC AGE GROUP:>10 - <18 years old					
n	6	4	1	5	11
Mean (SD)	27.2 (6.15)	30.5 (3.11)	24.0	29.2 (3.96)	28.1 (5.13)
Median	26	30	24	29	27
Range	21 - 39	28 - 35	24 - 24	24 - 35	21 - 39

(from page 22 of the Integrated Summary of Safety as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Run-in Phase

During the open-label run-in phase, all subjects were administered Pancreaze; the mean number of days of treatment with study drug was 10.1 days (range 4 to 20 days). The total subject-days of exposure was 577 days (please refer to the table below).

Table 19. Summary of Total Exposure for Run-in Phase by Treatment Group(Safety Analysis Set for Studies PNCRLPCYS3001 and 20-101)

Total Time on Drug Statistics	Total (N=57)
N	57
Mean (SD)	10.1 (4.59)
Median	11
Range	4 - 20
Total subject-days of exposure	577

(from page 22 of the Integrated Summary of Safety as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Thirty-one children/adolescents (<18 years old) were administered Pancreaze (refer to the table below please).

Table 20. Summary of Total Exposure for Run-in Phase in Children/Adolescents by Age Category and Treatment Group (Safety Analysis Set for Studies PNCRLPCYS3001 and 20-101)

PEDIATRIC AGE GROUP		PANCREASE MT (lipase units/kg/day)			
Total Time on Drug Statistics	Placebo (N=8)	<10,000 (N=22)	>=10,000 (N=1)	Total (N=23)	Total (N=31)
PEDIATRIC AGE GROUP:0 - 1 year old					
n	0	4	0	4	4
Mean (SD)		5.0 (0.00)		5.0 (0.00)	5.0 (0.00)
Median		5		5	5
Range		5 - 5		5 - 5	5 - 5
Total subject-days of exposure[a]	0	20	0	20	20
PEDIATRIC AGE GROUP:>1 - 5 years old					
n	0	13	0	13	13
Mean (SD)		5.0 (0.00)		5.0 (0.00)	5.0 (0.00)
Median		5		5	5
Range		5 - 5		5 - 5	5 - 5
Total subject-days of exposure[a]	0	65	0	65	65
PEDIATRIC AGE GROUP:>5 - 10 years old					
n	2	1	0	1	3
Mean (SD)	11.0 (2.83)	13.0		13.0	11.7 (2.31)
Median	11	13		13	13
Range	9 - 13	13 - 13		13 - 13	9 - 13
Total subject-days of exposure[a]	22	13	0	13	35
PEDIATRIC AGE GROUP:>10 - <18 years old					
n	6	4	1	5	11
Mean (SD)	13.5 (3.89)	11.0 (4.83)	10.0	10.8 (4.21)	12.3 (4.08)
Median	14	13	10	12	13
Range	8 - 18	4 - 15	10 - 10	4 - 15	4 - 18
Total subject-days of exposure [a]	81	44	10	54	135

[a] Subject-days are defined as the sum of the number of days for each subject who received a dose.
(from page 23 of the Integrated Summary of Safety as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

The 4 subjects 0 to 1 year old, and the 13 subjects >1 to 5 years old all received Pancreaze for 5 days; therefore, the mean in both groups was 5 days. The total subject-days of exposure was 20 days in subjects 0 to 1 year old and 65 days in subjects >1 to 5 years old. The mean number of days on study drug for the 3 subjects >5 to 10 years old was 11.7 days (range 9 to 13 days). The total subject-days of exposure was 35 days. The mean number of days on study drug for the 11 subjects >10 to <18 years old was 12.3 days (range 4 to 18 days) and total subject-days of exposure was 135 days.

Randomization Phase

During the randomization phase, 20 subjects were administered placebo; the mean number of days on study drug was 5.4 days (range 4 to 7 days). Thirty-seven subjects were administered Pancreaze, and the mean number of days on study drug was also 5.4 days (range 2 to 6 days). The total subject-days of exposure was 107 days in the placebo group and 200 days in the Pancreaze group (please refer to the table below). One subject was administered Pancreaze ≥10,000 lipase units/kg/day; this subject was administered study drug for 6 days during the randomization phase.

Table 21. Summary of Total Exposure for Randomization Phase by Treatment Group (Safety Analysis Set for Studies PNCRLPCYS3001 and 20-101)

		PANCREASE MT (lipase units/kg/day)			
Total Time on Drug Statistics	Placebo (N=20)	<10,000 (N=36)	>=10,000 (N=1)	Total (N=37)	Total (N=57)
N	20	36	1	37	57
Mean (SD)	5.4 (0.81)	5.4 (0.90)	6.0	5.4 (0.90)	5.4 (0.86)
Median	5	6	6	6	6
Range	4 - 7	2 - 6	6 - 6	2 - 6	2 - 7
Total subject-days of exposure[a]	107	194	6	200	307

[a] Subject-days are defined as the sum of the number of days for each subject who received a dose.
(from page 24 of the Integrated Summary of Safety as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Eight children/adolescents were administered placebo and 23 children/adolescents were administered Pancreaze during the randomization phase (see table below).

Table 22. Summary of Total Exposure for Randomization Phase in Children/Adolescents by Age Category and Treatment Group (Safety Analysis Set for Studies PNCRLPCYS3001 and 20-101)

PEDIATRIC AGE GROUP		PANCREASE MT (lipase units/kg/day)			
Total Time on Drug Statistics	Placebo (N=8)	<10,000 (N=22)	>=10,000 (N=1)	Total (N=23)	Total (N=31)
PEDIATRIC AGE GROUP:0 - 1 year old					
n	0	4	0	4	4
Mean (SD)		6.0 (0.00)		6.0 (0.00)	6.0 (0.00)
Median		6		6	6
Range		6 - 6		6 - 6	6 - 6
Total subject-days of exposure[a]	0	24	0	24	24
PEDIATRIC AGE GROUP:>1 - 5 years old					
n	0	13	0	13	13
Mean (SD)		5.7 (1.11)		5.7 (1.11)	5.7 (1.11)
Median		6		6	6
Range		2 - 6		2 - 6	2 - 6
Total subject-days of exposure[a]	0	74	0	74	74
PEDIATRIC AGE GROUP:>5 - 10 years old					
n	2	1	0	1	3
Mean (SD)	5.0 (0.00)	6.0		6.0	5.3 (0.58)
Median	5	6		6	5
Range	5 - 5	6 - 6		6 - 6	5 - 6
Total subject-days of exposure[a]	10	6	0	6	16
PEDIATRIC AGE GROUP:>10 - <18 years old					
n	6	4	1	5	11
Mean (SD)	5.3 (0.82)	4.8 (0.50)	6.0	5.0 (0.71)	5.2 (0.75)
Median	6	5	6	5	5
Range	4 - 6	4 - 5	6 - 6	4 - 6	4 - 6
Total subject-days of exposure[a]	32	19	6	25	57

[a] Subject-days are defined as the sum of the number of days for each subject who received a dose.
(from page 25 of the Integrated Summary of Safety as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

All 4 subjects 0 to 1 year old received Pancreaze for 6 days and the total subject-days of exposure was 24 days. All 13 subjects >1 to 5 years old received Pancreaze for a mean of 5.7 days (range 2 to 6 days); total subject-days of exposure was 74 days. Two of the 3 subjects >5 to 10 years old received placebo (both subjects received placebo for 5.0 days) and 1 subject in this age category received Pancreaze for 6 days. The total subject-days of exposure was 10 days for subjects receiving placebo and 6 days for the subject receiving Pancreaze. Six of the 11 children/adolescents >10 to <18 years old received placebo for a mean of 5.3 days (range 4 to 6 days) and 5 of the subjects in this age category received Pancreaze for a mean of 5 days (range 4 to 6 days). The total subject-days of exposure was 32 days for subjects receiving placebo and 25 days for subjects receiving Pancreaze. One pediatric subject was administered Pancreaze ≥10,000 lipase units/kg/day; this subject was administered study drug for 6 days during the randomization phase.

The Pancreaze clinical program was limited to short-term efficacy and safety studies which are acceptable as per the PEP Guidance. The long-term safety of PEPs has been established through

their use over the many years. This NDA application relied on the published medical literature pertaining to the full descriptions of the AE profiles.

7.2.2 Explorations for Dose Response

There were no formal dose-response investigations that were performed; however, all patients were titrated to relief of symptoms and remained within CFF guidelines.

7.2.3 Special Animal and/or In Vitro Testing

Since there has been 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 Pancreaze clinical development program. Additionally, this submission was a 505(b)(2) application, and therefore, no special animal or in vitro testing was required.

7.2.4 Routine Clinical Testing

The schedule of clinical assessments for each of the studies was adequate (please refer to the schedules of study visits for Studies PNCRLPCYS3001 and 20-101 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). Given that PEPs are not absorbed, no EKGs were obtained.

7.2.5 Metabolic, Clearance, and Interaction Workup

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

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

PEPs have had an extensive history or clinical use and their safety profile has been well described. Fibrosing colonopathy (FC) is the most serious safety concern with PEP administration and it 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 has developed were individuals who had been taking PEPs at high doses. As a result of this potential safety (and efficacy) concern, the CFF and FDA published weight-based dosing guidelines for PEP administration (see Section 2.4).

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

PEP treatment has been associated with elevated serum and urine levels of uric acid (hyperuricemia and hyperuricosuria). Uric acid levels were adequately monitored in Study PNCRLPCYS3001. 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.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in any of the three studies (PNCRLP-CYS-1001, 20-101, and PNCRLPCYS3001).

7.3.2 Nonfatal Serious Adverse Events

Study 20-101

No serious adverse events were reported during this study. No subjects withdrew from the study due to adverse events.

Study PNCRLPCYS3001

No subject reported a serious adverse event during the study. One subject who was administered Pancreaze experienced an adverse event leading to study discontinuation during the open-label phase of the study (please refer to the table below). This subject was not randomized into the double-blind phase of the study. Subject 001018-011801 (abdominal pain) was a 17-year-old white female with cystic fibrosis and pancreatic insufficiency. The subject had a medical history of asthma, pulmonary exacerbation, allergic rhinitis, chronic sinusitis, GERD, constipation, and Tourette Syndrome. Concomitant medications at entry into the study included levosalbutamol, dornase alfa, and tobramycin inhalers; mometasone furoate, cetirizine HCl, montelukast, ranitidine HCl, bisacodyl, and macrogol. The subject's previous enzyme preparation was Nortase. The subject was entered into the screening phase of the study and was administered Pancreaze 10.5 (5 capsules with meals [three times a day, tid] and 2 capsules with snacks [twice a day, bid]) for 7 days. Laboratory analysis on Day 6 revealed increased fat in stool (24 g/specimen) and increased %fat (21%). On Day 7, the subject reported mild abdominal pain lasting 3 days. The study drug was discontinued and the subject was withdrawn from the study. The event was assessed by the investigator to be unrelated to Pancreaze administration.

Table 23. Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Medication (All Enrolled Analysis Set in Study PNCRLPCYS3001)

System Organ Class/ Preferred Term	PLACEBO (N=20)	PANCREASE MT (N=20)	NOT RANDOMIZED (N=5)	TOTAL (N=45)
Subjects with at least one TEAE Started Before Double-Blind	0	0	1(20%)	1(2%)
Gastrointestinal disorders/	**0**	**0**	**1(20%)**	**1(2%)**
Abdominal pain	0	0	1(20%)	1(2%)

(from page 63 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

7.3.3 Dropouts and/or Discontinuations

Study 20-101

For a description of patient dropouts/withdrawals, please refer to Section 6.1.3.

The table below summarizes the number and percent of subjects who withdrew early from the randomized period of the study. Subjects were counted only once by primary reason. The following order of reasons for withdrawal was used to assign a primary reason for withdrawal: adverse event, protocol violation, parent withdrew consent, subject lost to follow-up, use of prohibited concomitant medication and other. One subject was withdrawn initially from the total subjects enrolled (N=18) due to parental consent withdrawal and another subject, in the 1000 units lipase/kg/meal group, discontinued prematurely from the randomized study period due to consent withdrawal by parent.

Table 24. Distribution of Subjects Who Withdrew Prematurely During the Open-Label Run-in Period, by Primary Reason for Withdrawal– All Subjects Enrolled

Reason for Withdrawal[a]	(N=18) n (%)
Adverse Event	0 (0.0%)
Protocol Violation	0 (0.0%)
Parent Withdrew Consent	1 (5.6%)
Subject Lost to Follow-Up	0 (0.0%)
Use Prohibited Concomitant Medication	0 (0.0%)
Other	0 (0.0%)

a: Subjects were counted once, under their primary reason for withdrawal.

Study PNCRLPCYS3001

54 subjects were screened for entry into the study, and 5 of these subjects failed screening procedures. The remaining 49 subjects were enrolled; from these enrolled subjects, 9 subjects discontinued from the study prior to randomization for the following reasons:

- 2 subjects withdrew consent (1 prior to receiving open-label study drug)

- adverse event (1 subject) –already discussed in section 7.3.3
- noncompliance with study drug (1 subject)
- "other reasons" (5 subjects); these 5 subjects had percent CFA values that were ≤80% (48%. 59.8%, 64.2%, and 77.1%), or were not obtained, and therefore, did not meet randomization criteria

The remaining 40 subjects were randomized in a 1:1 fashion to receive either Pancreaze or placebo. All 40 subjects completed the study (please refer to the table below and Section 6.1.3).

Table 25. Summary of Subject Disposition (All Enrolled Study Subjects in Study PNCRLPCYS3001)

	PANCREASE MT	Placebo	Not randomized	Total
Number of subjects enrolled	20	20	9	49
Number of subjects randomized	20	20	0	40
Number of subjects entered the study				
Number of subjects entered run-in	20	20	8	48
Number of subjects entered double-blind	20	20	0	40
Number of subjects included in ITT population	20	20	0	40
Number of subjects included in per-protocol population	20	19	0	39
Number of subjects included in completers population	20	20	0	40
Number of subjects completed the study	20	20	0	40

(from page 36 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

No subjects discontinued from the study due to an adverse event during the double-blind phase of this study.

7.3.4 Significant Adverse Events

Study 20-101

There were no significant adverse events reported in this study.

Study PNCRLPCYS3001

There were no significant adverse events reported in this study.

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.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study 20-101

The number and percent of subjects with adverse events during the randomized period by system organ class and MedDRA preferred term for all randomized subjects are shown in the table below.

Table 26 Number and Percent of Subjects with Adverse Events During The Randomized Period by System Organ Class and MedDRA Preferred Term – All Randomized Subjects

System Organ Class MedDRA Preferred Term	375 units Lipase/kg/meal N=4	750 units Lipase/kg/meal N=5	1125 units Lipase/kg/meal N=4	1500 units Lipase/kg/meal N=4
Any Adverse Event	1 (25.0)	1 (20.0)	0 (0.0)	2 (50.0)
Gastrointestinal Disorders	1 (25.0)	1 (20.0)	0 (0.0)	1 (25.0)
Abdominal Pain	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal Faeces	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Frequent Bowel Movements	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)
Respiratory, Thoracic And Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)
Increased Bronchial Secretion	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)

(modified from page 109 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Gastrointestinal disorders (abdominal pain, abnormal feces, constipation, frequent bowel movements, and vomiting) were the most frequently reported adverse events, and all gastrointestinal events were considered mild.

Study PNCRLPCYS3001

One subject administered Pancreaze experienced an adverse event leading to study discontinuation during the open-label phase of the study (please refer to Section 7.3.2); this subject was not randomized into the double-blind phase. A detailed narrative is provided in section 7.3.2. No subjects discontinued from the study due to an adverse event during the double-blind phase of the study.

During the double-blind phase, 12 subjects (60%) receiving placebo and 8 subjects (40%) receiving Pancreaze reported at least 1 adverse event (please refer to the table below). The most common event was abdominal pain, reported in 3 placebo subjects (15%) and 2 Pancreaze subjects (10%).

Table 27 Summary of Treatment-Emergent Adverse Events During the Double-Blind Phase (Safety Analysis Set in Study PNCRLPCYS3001)

System Organ Class/ Preferred Term	PLACEBO (N=20)	PANCREASE MT (N=20)	TOTAL (N=40)
Subjects with at Least one TEAE Started After Double-Blind	12(60%)	8(40%)	20(50%)
Gastrointestinal disorders/	**11(55%)**	**6(30%)**	**17(43%)**
Abdominal pain	3(15%)	2(10%)	5(13%)
Abdominal pain upper	3(15%)	1(5%)	4(10%)
Diarrhoea	4(20%)	0	4(10%)
Flatulence	3(15%)	1(5%)	4(10%)
Abnormal faeces	3(15%)	0	3(8%)
Abdominal discomfort	1(5%)	0	1(3%)
Abdominal distension	1(5%)	0	1(3%)
Dyspepsia	0	1(5%)	1(3%)
Gastric disorder	0	1(5%)	1(3%)
Vomiting	0	1(5%)	1(3%)
General disorders and administration site conditions/	**3(15%)**	**0**	**3(8%)**
Fatigue	2(10%)	0	2(5%)
Asthenia	1(5%)	0	1(3%)
Feeling cold	1(5%)	0	1(3%)
Thirst	1(5%)	0	1(3%)
Infections and infestations/	**0**	**1(5%)**	**1(3%)**
Influenza	0	1(5%)	1(3%)
Metabolism and nutrition disorders/	**1(5%)**	**0**	**1(3%)**
Decreased appetite	1(5%)	0	1(3%)
Musculoskeletal and connective tissue disorders/	**1(5%)**	**0**	**1(3%)**
Arthralgia	1(5%)	0	1(3%)
Pain in extremity	1(5%)	0	1(3%)
Nervous system disorders/	**0**	**1(5%)**	**1(3%)**
Headache	0	1(5%)	1(3%)
Psychiatric disorders/	**0**	**1(5%)**	**1(3%)**
Anxiety	0	1(5%)	1(3%)
Reproductive system and breast disorders/	**0**	**1(5%)**	**1(3%)**
Dysmenorrhoea	0	1(5%)	1(3%)
Respiratory, thoracic and mediastinal disorders/	**0**	**1(5%)**	**1(3%)**
Respiratory disorder	0	1(5%)	1(3%)
Vascular disorders/	**1(5%)**	**0**	**1(3%)**
Pallor	1(5%)	0	1(3%)

Note: Every subject is counted once within treatment group, System Organ Class and Preferred Term. The sorting is done by decreasing frequency of SOC, then by preferred term in the Total column.
(from page 61 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

7.4.2 Laboratory Findings

Study 20-101

No laboratory data were collected during this study.

Study PNCRLPCYS3001

Changes in laboratory values were seen from screening through the end of the study. Changes between the 2 treatment groups were similar, with the following exceptions: median alkaline phosphatase values in placebo subjects increased 8.5 U/L, while median values in Pancreaze subjects decreased by 3.0 U/L; median platelets in placebo subjects increased 10 $x10^9$/L while median values in Pancreaze subjects decreased 13.5 $x10^9$/L. These changes were not considered clinically relevant. The changes reflected in hemoglobin most likely reflect some hemo-concentration in placebo subjects due to increased fluid losses from increased stool output, although blood urea nitrogen did not change significantly between placebo and Pancreaze treatment arms. Please refer to the table below for the above observations.

Table 28 Summary of Laboratory Evaluations by Lab Panel – Change From Screening (Safety Analysis Set in Study PNCRLPCYS3001)

LAB PANEL **Laboratory Analyte** Statistics	PLACEBO (N=20)	PANCREASE MT (N=20)	TOTAL (N=40)
CHEMISTRY			
Alanine Aminotransferase (U/L)			
N	20	19	39
Mean (SD)	4.5(46.55)	4.4(15.28)	4.4(34.55)
Median	5.0	2.0	4.0
Range	-157.0 - 115.0	-19.0 - 40.0	-157.0 - 115.0
Alkaline Phosphatase (U/L)			
N	20	19	39
Mean (SD)	10.0(25.14)	-14.7(32.97)	-2.1(31.43)
Median	8.5	-3.0	5.0
Range	-31.0 - 76.0	-103.0 - 19.0	-103.0 - 76.0
Bilirubin (umol/L)			
N	20	19	39
Mean (SD)	1.6(4.31)	-0.2(2.73)	0.7(3.70)
Median	1.7	0.0	0.0
Range	-5.1 - 10.3	-5.1 - 5.1	-5.1 - 10.3
Blood Urea Nitrogen (mmol/L)			
N	20	19	39
Mean (SD)	-1.1(1.51)	0.2(1.28)	-0.5(1.55)
Median	-0.9	0.4	-0.4
Range	-4.6 - 1.1	-2.5 - 2.1	-4.6 - 2.1
Creatine Kinase (U/L)			
N	20	19	39
Mean (SD)	-10.2(41.73)	9.7(63.88)	-0.5(53.90)
Median	-12.5	-6.0	-11.0
Range	-94.0 - 118.0	-108.0 - 209.0	-108.0 - 209.0
Triglycerides (mmol/L)			
N	20	19	39
Mean (SD)	0.1(0.43)	0.5(0.84)	0.3(0.69)
Median	0.1	0.1	0.1
Range	-1.1 - 0.7	-0.2 - 3.0	-1.1 - 3.0
HEMATOLOGY			
Hemoglobin (g/L)			
N	19	20	39
Mean (SD)	3.8(6.94)	1.2(5.27)	2.5(6.20)
Median	4.0	1.0	2.0
Range	-9.0 - 20.0	-9.0 - 11.0	-9.0 - 20.0
Platelets ($x10^9$/L)			
N	19	20	39
Mean (SD)	6.2(32.77)	-20.4(50.75)	-7.4(44.47)
Median	10.0	-13.5	-6.0
Range	-63.0 - 54.0	-162.0 - 70.0	-162.0 - 70.0

Note: Values include subjects who had data at the two time points (screening and end of study).

(from page 65 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

7.4.3 Vital Signs

Study 20-101

Blood pressure and pulse measurements were collected at screening or Visit 1 (Day 1), randomization or Visit 2 (Day 6) and Visit 3 (Day 11). There were no clinically important changes in vital signs within any treatment group during the five-day randomized treatment period. There were no clinically important differences among treatment groups in the changes in systolic and diastolic blood pressure and pulse from randomization to the end of study. Mean

changes from Visit 2 in systolic blood pressure, diastolic blood pressure and pulse at Visit 3 for all enrolled subjects were -4.0 mmHg, -8.0 mmHg and -1.1 beats/minute, respectively.

Table 29 Change in Systolic and Diastolic Blood Pressure (mm Hg) and Pulse (beats/min) from Visit 2 at Visit 3 – All Subjects Enrolled

	375 units Lipase/kg/meal	750 units Lipase/kg/meal	1125 units Lipase/kg/meal	1500 units Lipase/kg/meal	All Subjects Enrolled[b]
Change in Systolic Blood Pressure (mmHg) from Visit 2 at Visit 3					
n	4	3	3	4	14
Mean (SD)	-1.3 (9.74)	3.7 (6.81)	-0.7 (11.59)	-15.0 (18.51)	-4.0 (13.58)
Median	-2.0	6.0	1.0	-8.0	-3.0
(Min,Max)	(-12.0, 11.0)	(-4.0, 9.0)	(-13.0, 10.0)	(-42.0, -2.0)	(-42.0, 11.0)
Change in Diastolic Blood Pressure (mmHg) from Visit 2 at Visit 3					
n	4	3	3	4	14
Mean (SD)	-1.5 (5.51)	-4.7 (2.52)	-16.3 (14.57)	-10.8 (13.60)	-8.0 (10.83)
Median	-2.0	-5.0	-18.0	-10.0	-6.0
(Min,Max)	(-7.0, 5.0)	(-7.0, -2.0)	(-30.0, -1.0)	(-28.0, 5.0)	(-30.0, 5.0)
Change in Pulse (bpm) from Visit 2 at Visit 3					
n	4	3	3	4	14
Mean (SD)	5.5 (5.26)	-12.0 (26.85)	-1.7 (10.41)	0.8 (37.85)	-1.1 (22.51)
Median	6.0	-7.0	-5.0	9.0	1.0
(Min,Max)	(0.0, 10.0)	(-41.0, 12.0)	(-10.0, 10.0)	(-51.0, 36.0)	(-51.0, 36.0)

b: All subjects enrolled includes one subject who was not randomized to any treatment group after withdrawal from the study

(modified from page 117 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

Change in respiration, temperature, and length is shown in the table below.

Table 30. Change in Respiration (breaths/minute), Temperature (°C), and Length (cm) – All Subjects Enrolled

	375 units Lipase/kg/meal	750 units Lipase/kg/meal	1125 units Lipase/kg/meal	1500 units Lipase/kg/meal	All Subjects Enrolled[b]
Change in Respiration (bpm) from Visit 2 at Visit 3					
n	4	4	4	4	16
Mean (SD)	1.8 (10.90)	0.0 (2.94)	-7.5 (15.09)	1.3 (1.50)	-1.1 (9.29)
Median	-3.0	-0.5	-1.0	1.0	0.0
(Min,Max)	(-5.0, 18.0)	(-3.0, 4.0)	(-30.0, 2.0)	(0.0, 3.0)	(-30.0, 18.0)
Change in Temperature (°C) from Visit 2 at Visit 3					
n	4	3	4	3	14
Mean (SD)	-0.1 (0.56)	0.0 (0.36)	-0.3 (0.49)	0.3 (0.10)	-0.1 (0.45)
Median	0.1	-0.1	-0.4	0.3	0.1
(Min,Max)	(-0.9, 0.4)	(-0.3, 0.4)	(-0.8, 0.3)	(0.2, 0.4)	(-0.9, 0.4)
Change in Length (cm) from Visit 1 at Visit 3					
n	4	4	4	4	17
Mean (SD)	1.2 (1.69)	0.8 (0.87)	0.4 (0.76)	0.6 (1.08)	0.7 (1.07)
Median	0.4	0.7	0.1	0.5	0.3
(Min,Max)	(0.2, 3.7)	(0.0, 2.0)	(-0.2, 1.5)	(-0.4, 2.0)	(-0.4, 3.7)

b: All subjects enrolled includes one subject who was not randomized to any treatment group after withdrawal from the study

(modified from page 119 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

There were no clinically significant changes in respiration or temperature within any treatment group during the five-day randomized treatment period and no clinically significant changes in length within any treatment group during the course of the study. In addition, there were no clinically significant differences among treatment groups in the changes in respiration or temperature from randomization to the end of study or in length from Visit 1 to the end of study. Mean changes in respiration and temperature at Visit 3 were -1.1 breaths per min and -0.1 ºC, respectively, from Visit 2. Mean change in length from Visit 1 at Visit 3 was 0.7 cm.

Study PNCRLPCYS3001

There were no notable differences in the changes in vital sign measurements from screening to the end of study between the 2 treatment groups, and there were no clinically meaningful vital sign measurements noted during the study (please refer to the table below).

Table 31. Summary of Vital Signs – Change From Screening (Safety Analysis Set in Study PNCRLPCYS3001)

Measurement Statistics	PLACEBO (N=20)	PANCREASE MT (N=20)	TOTAL (N=40)
Diastolic Blood Pressure mmHG - change from screening[a]			
N	20	20	40
Mean (SD)	1.8(7.08)	-1.3(11.78)	0.2(9.72)
Median	0.5	-4.5	0.0
Range	-14.0 - 16.0	-20.0 - 25.0	-20.0 - 25.0
Height cm - change from screening[a]			
N	20	20	40
Mean (SD)	0.2(1.03)	0.7(1.41)	0.4(1.24)
Median	0.0	0.0	0.0
Range	-2.0 - 2.7	-1.0 - 4.9	-2.0 - 4.9
Pulse beats/min - change from screening[a]			
N	20	20	40
Mean (SD)	-0.5(3.87)	-0.2(4.20)	-0.3(3.99)
Median	0.0	0.0	0.0
Range	-8.0 - 8.0	-10.0 - 6.0	-10.0 - 8.0
Systolic Blood Pressure mmHG - change from screening[a]			
N	20	20	40
Mean (SD)	-0.4(12.18)	3.5(10.52)	1.6(11.40)
Median	-1.5	3.0	2.0
Range	-20.0 - 24.0	-18.0 - 27.0	-20.0 - 27.0
Temperature C - change from screening[a]			
N	20	20	40
Mean (SD)	0.0(0.64)	-0.4(0.82)	-0.2(0.76)
Median	-0.1	-0.3	-0.2
Range	-1.0 - 1.2	-2.2 - 1.2	-2.2 - 1.2

[a] Includes subjects who had data at the two time points.

(from page 66 of Clinical Study Report as released by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)

7.4.4 Electrocardiograms (EKGs)

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

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed in the Pancreaze clinical development program.

7.4.6 Immunogenicity

Pancreaze and other porcine-derived PEPs are not systemically absorbed, and immunogenicity testing was not performed as part of the EUR-1008 clinical development program.

7.5 Other Safety Explorations

No other safety explorations were performed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Pancreaze 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 Pancreaze were conducted in pregnant women. However, it is quite likely that Pancreaze will be used by pregnant women and women of reproductive potential in the future. Since PEPs have been available in the market prior to 1938, it is highly possible that they have been used by pregnant women in the past. Given that PEPs are not absorbed, no known effects of active ingredients on pregnant women or their offspring have been recorded; therefore, any future labeling should address safety in pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

PEPs are recognized as having a positive effect on growth in pediatric patients with CF[6,7]. Studies performed in the Pancreaze clinical development program were short-term studies; these short-term studies followed the recommendations for study designs as recommended in the

[6] 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)
[7] Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol. 2006;20(3):531-46. (PMID: 1470282)

Guidance for submitting PEP NDAs, and therefore, long-term growth and development amongst the pediatric population were not assessed.

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.

One important safety issue regarding the use of PEPs is fibrosing colonopathy (FC). The etiology of FC has not been clearly established, but it has been hypothesized to be associated with high dose lipase exposure.[6,7] The Cystic Fibrosis Foundation (CFF), in conjunction with the FDA, has recommended starting lipase doses according to age in order to optimize therapy while minimizing the risk of FC. These recommendations are described below.

The CFF recommends the following dose schedule for full meals:

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

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 Pancreaze and for all PEPs.

In addition, it should be noted that there was one patient in Study PNCRLPYS3001 who received a dose higher than 10,000 lipase units per kilogram per day. This was a 10 year-old male patient administered a Pancreaze dose of 12,399 lipase units per kilogram per day for the duration of the open-label and randomized withdrawal periods; the patient also received daily doses during screening that were elevated. The patient had a past medical history significant for cystic fibrosis, chronic sinusitis, gastroesophageal reflux, malabsorption, and reactive airways disease. The patient required higher doses based on pre-study doses required to alleviate steatorrhea as determined by the Principal Investigator. The patient experienced mild abdominal pain throughout both study periods. Abnormal chemistry data at the end of the study included the following elevations:

- aspartate aminotransferase (AST): 27 U/L (at screening); 67 U/L (at Visit 4)
- alanine aminotransferase (ALT): 34 U/L (at screening); 92 U/L (at Visit 4)
- serum phosphate: 1.81 mmol/L(at screening); 1.74 mmol/L (at Visit 4)

Abnormal hematology data at the end of the study included:

- hematocrit: 46% (at screening); 43% (at Visit 4)

No abnormalities from analyses of urinalysis or uric acid were noted.
(See also Section 7.2.1.)

7.7 Additional Submissions

The sponsor's response to a clinical information request was received on March 9, 2010. The sponsor responded to questions about the following (in the pivotal study): (1) proportion of patients experiencing gastrointestinal adverse events; (2) adverse events occurring at a frequency greater than 10% in either the placebo or the Pancreaze group; (3) information about a patient receiving greater than 10,000 Units/lipase/kg/day (see Section 7.6); and (4) the point estimate and 95% confidence interval of the treatment difference for the primary endpoint of change in CFA from the open label period to the end of the double-blind withdrawal period. Each of these analyses provided by the sponsor was reproduced by the reviewers.

8 Postmarket Experience

Pancreaze (marketed as "Pancrease MT") has been available since 1988 and much clinical data regarding its safety and efficacy are available. The active ingredient in Pancreaze, pancrelipase, is presently widely available from several different manufacturers as enteric coated (EC) and non-EC formulations (which are not interchangeable). Many different PEP formulations are currently available in the United States and worldwide. Overall, the safety information reported in the Pancreaze clinical development program is consistent with the safety profile of PEPs reported in the published literature, and no additional safety information from this worldwide experience, other than as noted in this review (e.g., FC, hyperuricemia, and hyperuricosuria), is to be included in product labeling.

9 Appendices

9.1 Literature Review/References

Please see individual references noted throughout this review.

9.2 Labeling Recommendations

This NDA is recommended to receive an Approval action and the labeling is presently being negotiated with the Sponsor during this review cycle.

9.3 Advisory Committee Meeting

No Advisory Committee was convened for this application.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22523	ORIG-1	JOHNSON & JOHNSON PHARMACEUTICAL RESEARCH & DEVELOPMENT LLC	Pancrelipase Microtablets

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

/s/

ALI NIAK
04/12/2010

ANIL K RAJPAL
04/12/2010
I concur with Dr. Niak.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-523 **Applicant: Johnson & Johnson** **Stamp Date: 06-25-09**

Drug Name: Pancrease MT **NDA/BLA Type:NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505b(2)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: PNCRLPCYS3001 Indication: treatment of exocrine pancreatic insufficiency due to cystic fibrosis or	X			See Pancreatic Enzyme Products Guidance <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf>

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	other conditions				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			See Pancreatic Enzyme Products Guidance <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf>
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Ali Niak	08-19-09
Reviewing Medical Officer	Date
Anil Rajpal	08-19-09
Clinical Team Leader	Date

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

/s/

ALI NIAK
08/19/2009

ANIL K RAJPAL
08/19/2009