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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-523
Drug Name:	Pancrease MT (pancrelipase micro tablets)
Indication(s):	Treatment of Cystic Fibrosis-Dependent Exocrine Pancreatic Insufficiency
Applicant:	Johnson & Johnson Pharmaceutical Research Dev. LLC
Date(s):	Stamp: June 23, 2009 PDUFA: April 04, 2010
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Shahla S. Farr, M.S.
Concurring Reviewer:	Mike Welch, Ph.D.
Medical Division:	Division of Gastroenterology Products
Clinical Team:	Ali Niak, M.D., Anil Rajpal, M.D. (TL)
Project Manager:	Stacy Barley, RN, M.S.N., M.H.A.

Keywords: NDA review, clinical study, randomized withdrawal study

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

From the statistical perspective, the data from Study PNCRLPCYS3001 indicate that Pancrease MT is effective for treatment of adult and children/adolescent subjects with CF-dependent exocrine pancreatic insufficiency.

1.2 Brief Overview and Background

The applicant has submitted one Phase 3, multi-center (US and Canada) randomized, two-arm, double-blind, placebo-controlled withdrawal study (Study # PNCRLPCYS3001) in subjects with CF-dependent exocrine pancreatic insufficiency. A total of 40 subjects (22 males and 18 females) were randomized into the study. Subjects had a percent COA-fat of 80% or more established at baseline. The primary analysis efficacy endpoint is the change in percent coefficient of fat absorption (COA-fat) from the 72-hour stool collection period at the end of the open-label baseline phase to the 72-hour stool collection period at the end of the randomized, double-blind withdrawal phase.

1.3 Statistical Issues and Findings

No major issues were observed in the review of this NDA. An analysis by gender sub-populations showed that the female subjects in the Placebo arm had a smaller decrease in their COA-fat than their male counterparts, although both gender subgroups indicated a statistically significant treatment effect.

2. INTRODUCTION

2.1 Overview

Cystic fibrosis (CF) is the most common autosomal recessive genetic disorder affecting Whites. The prevalence of CF in the US is 1 in 3,000 births and there are more than 30,000 patients in the US and 40,000 patients worldwide who are affected by the disorder. There is a strong correlation between the genetic mutation in CF and pancreatic sufficiency (PS) or Pancreatic Insufficiency (PI). The majority of patients with CF have PI, which manifests as mal-absorption.

Pancrease MT (pancrelipase) enteric-coated, delayed-release capsules are pancreatic enzyme supplements for oral administration. Pancreatic enzyme therapy acts locally within the duodenum and digests macronutrients, including fats, carbohydrates, and protein. Pancrease MT has been marketed since 1988 and has been used by patients with cystic fibrosis (CF) and chronic pancreatitis.

Pancrease MT has been marketed since 1988 and has been used by patients with cystic fibrosis (CF) and chronic pancreatitis. On 28 April 2004 the FDA announced that all exocrine pancreatic insufficiency (EPI) drug products require an approved New Drug Application (NDA) by 28 April 2008, for continued marketing. The FDA extended this date to 28 April 2010, provided that the sponsors have an active Investigational New Drug Application (IND) by 28 April 2008 and have submitted NDAs by 28 April 2009.

To fulfill these requirements and confirm the safety and efficacy of PANCREASE MT, the applicant has submitted one Phase 3, multi-center (US and Canada) randomized, double-blind, placebo-controlled withdrawal study (Study # PNCRLPCYS3001) in subjects with CF-dependent exocrine pancreatic insufficiency.

2.2 Data Sources

This NDA was submitted in electronic format and is located at:

\\Cdsesub1\evsprod\NDA022532.enx

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Primary Objective

The primary objective of the study was to establish the efficacy and safety of Pancrease MT delayed-release capsules (MT 10.5 or MT 21) on the quantitative change in fat absorption in adults and children/adolescent subjects with cystic fibrosis who had clinical symptoms of exocrine pancreatic insufficiency.

Study Design

This was a phase 3, multi-center (US and Canada) randomized, double-blind, placebo-controlled withdrawal study (Study # PNCRLPCYS3001) in subjects with CF-dependent exocrine pancreatic insufficiency. A total of 40 subjects (22 males and 18 females) are randomized into the study. Fourteen subjects (35%) were between the ages of 7 to 17 years and 26 subjects (65%) were in the 18 to 60 age category. In withdrawal trials, incorporation of early escape mechanisms and explicit study withdrawal criteria decrease the duration of patients' exposure to placebo alone.

This multicenter study consisted 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 PANCREASE MT 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 PANCREASE MT 10.5 or MT 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. On the basis of the COA-fat percentage calculated from the number of fat grams ingested and the number of fat grams excreted in the 72-hour stool collection period of the open-label phase, subjects with a percent COA-fat of ≥80% were eligible for random assignment in the double-blind (withdrawal) phase of the study. Subjects who qualified for randomization (based on results of the fecal fat analysis) were randomly assigned (1:1) to receive placebo or PANCREASE MT 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.

Stools were collected for the determination of fat and protein (nitrogen) content during the final 72 hours of the high-fat period for both the open-label and double-blind (withdrawal) phases. Fat intake (dietary fat) and fat excretion (fecal fat) data were used to calculate fecal fat excretion per 24 hours, which was determined from the 72-hour stool collection. The percent coefficient of protein absorption (COA-protein) (nitrogen) was determined from the same stool collection periods at the end of the assay period. The stool collection period could be extended beyond the 72-hour period depending on the appearance of the dye marker; the first blue-tinted stool after taking the second dye marker may have appeared on Days 6, 7, or 8.

Primary Efficacy Endpoints

The primary analysis efficacy endpoint is the change in percent coefficient of fat absorption (COA-fat) from the 72-hour stool collection period at the end of the open-label phase to the 72-hour stool collection period at the end of the randomized, double-blind withdrawal phase. Percent COA-fat was calculated as the following percentage:

Percent COA-fat ={[Fat intake (grams) – Fat excretion (grams)]/Fat intake (grams)}x 100

Secondary Endpoints

A key secondary endpoint is COA-protein. The efficacy measure relative to COA-protein is the change in COA-protein from the 72-hour inpatient period in the open label phase to the 72-hour inpatient period in the randomized, double-blind (withdrawal) phase.

COA-protein ={[Protein intake {grams} – Protein excretion {grams}/Protein intake (grams)}x 100

Other secondary endpoints of this study included improvement in clinical signs and symptoms of EPI: nausea, vomiting, bloating, diarrhea, greasy stools and abdominal pain. Other secondary endpoints were based on stool diary, CGI-S, CGI-C, and GAC results.

In regards to these secondary endpoint variables, the sponsor is only seeking labeling on the change from baseline in protein absorption. Moreover, the clinical review team has indicated these other secondary endpoints are not of interest. Therefore, in this review, the only secondary endpoint analyzed is COA-protein.

Randomization and Blinding

Subjects eligible for the double-blind (withdrawal) phase were randomly assigned to 1 of 2 treatment groups (placebo or PANCREASE MT) in a 1:1 ratio based on a computer-generated randomization schedule prepared by the sponsor before the study.

The treatment allocation was made based on a randomly permuted blocks procedure. Based on this randomization code, the study drug was packaged and labeled for each subject. Subject numbers were assigned as subjects qualified for the study and were assigned to treatment.

Sample Size Calculation

Assuming the early withdrawal rate in this study was to be similar to an earlier study (20-101), the sponsor estimated that, with 18 subjects per group (a total of 36 subjects) who complete the study, at least 90% power would be achieved in rejecting the null hypothesis that there is no difference between the active and the placebo groups. This calculation was based on the assumption that the true mean difference between the active and the placebo group was 31.2% with a common standard deviation of 22.6% using a 2-sided, 2-sample, t-test with a 5% significance level. With the assumption of an early withdrawal rate of 10%, approximately 40 subjects (i.e., 20 subjects per treatment group) were randomized into the study.

Analysis Population and Subjects' Allocation

The primary efficacy population was the Intent-to-Treat (ITT) analysis set. To support the results from the ITT analysis set, an additional analysis of the primary efficacy endpoint was also to be performed on the Per-protocol (PP) analysis set.

The ITT analysis set included all subjects who were randomly assigned into the double-blind (withdrawal) phase of the study; and the PP analysis set is a subset of ITT that excludes subjects with major protocol violations (determined by reviewing protocol deviation study data without information of

associated treatment groups). Since all subjects finished the study and there were no withdrawals, in this study, the Completers Analysis Set was identical to the ITT and is not presented.

In the first protocol amendment the sponsor had indicated that the analyses of efficacy were to be performed for the ITT population and that the PP population was to be used as a sensitivity analyses; However, in the final submission, the primary statistical analysis was done using the Per-Protocol (PP) population; and a sensitivity analysis was performed for the ITT population. In this review, we performed our analyses based on both the populations. We are reporting the data for ITT and PP populations, as well as all randomized subjects.

Statistical Methodology

All statistical tests were interpreted at the 5% significance level (2-tailed), unless otherwise specified. The last observation carry forward (LOCF) approach was used to impute missing data for the ITT analysis. For any subject with missing percent COA-fat data at the end of the double-blind (withdrawal) phase, his/her baseline COA-fat value was to be used for imputation. Since all ITT subjects completed the double-blind phase, no missing data imputation was implemented for the percent COA-fat analysis.

Hypothesis: PANCREASE MT capsules (MT10.5 or MT21) are more effective than placebo as measured by the change in the coefficient of fat absorption (COA-fat) in adults and children/adolescent subjects with EPI secondary to CF.

To evaluate and compare the change in percent COA fat among the treatment groups, the sponsor used an ANCOVA model with treatment as a factor and baseline percent COA fat as a covariate for the Per Protocol set. In respond to FDA request on January 16, 2008 meeting, a sensitivity analysis was also performed with the inclusion of age as a factor in addition to treatment group and baseline COA-fat in the ANCOVA model.

Change of Age Groups

In the original protocol, age categories were defined as 7 to 18 years for children/adolescent and over 18 years for adults. In protocol Amendment 1 (2 April 2008), age categories were corrected to 7 to 17 for children/adolescent and 18 or more for adults. In the final analysis, the age categories were revised to follow the protocol amendment.

3.2 Efficacy Results

Subjects' Disposition, Demographics and Baseline Characteristics

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. 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 PANCREASE MT or placebo, where 38 were from the US and 2 from Canada. All 40 subjects completed the study.

For "Disposition of Subjects" table refer to the Table 1 of the Appendix.

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 5 subjects for "other reasons". These 5

subjects had either percent COA-fat values that were less than 80% (48%, 59.8%, 64.2%, and 77.1%) or the percent COA-fat values were not obtained and therefore did not meet randomization criteria.
The majority of the subjects in the study were male (55%), 18 or more years old (65%), and White (90%). 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 COA-fat at baseline was 89.4% (4.88%) overall, and no notable differences in mean percent COA-fat between treatment groups. There was an imbalance between the sexes of subjects in the placebo group: 65% males and 35% females.

For "Demographics and Baseline Characteristics" tables refer to Table 2 of the Appendix.

Analyses of the Primary Endpoints

The "all randomized subjects" population is the same as the ITT group. Table 1 shows the results of the primary efficacy variable, the change from baseline in the mean of COA-fat for both arms.

Table 1: Results of the Primary Endpoint Variable, Change from Baseline in the Mean of COA-fat

Treatment Arm	N	Baseline Mean (SD)	EOT Mean (SD)	Difference Mean (SD)	P-Value for the Difference
Pancrease MT	20	88.22 (5.07)	86.77 (8.09)	1.45 (5.88)	<0.001
Placebo	20	90.51 (4.51)	56.37 (24.93)	34.14 (23.03)	

The sponsor excluded one subject in the Pancrease MT arm because of a major protocol deviation. These analyses were repeated for the PP population. The results were consistent to that of the ITT.

Analyses of the Secondary Endpoint COA-Protein

Table 2 shows the results for this secondary endpoint variable.

Table 2: Analysis of COA-Protein

Treatment Arm	N	Baseline Mean (SD)	EOT Mean (SD)	Difference Mean (SD)	P-Value for the Difference
Pancrease MT	20	81.16 (6.42)	82.42 (6.00)	1.26 (4.71)	<0.001
Placebo	20	84.48 (7.78)	57.95 (19.73)	-26.54 (15.30)	

As it is shown in Table 2, the difference in treatment group means was statistically significant ($p<0.001$).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age and Other Special/Subgroup Populations

Out of the forty subjects in this clinical trial, only 2 subjects were from Canada (both in placebo arm); the rest (38 subjects) were from the US. In addition, only one African American subject had participated in

this study. Therefore, no subgroups analyses by country or race were performed. The sample sizes for these sub-populations were not large enough to justify reasonable subgroup efficacy analyses of interest.

We performed an ANCOVA including gender and baseline COA-fat as the factors in the model. There was a statistically significant treatment-by-gender interaction (p=0.004). Therefore, we proceeded to analyze the data by gender to get a closer look at this difference in treatment. Table 3 shows the results.

Table 3: Analysis of COA-Fat by Gender - Mean (Std)

Gender	Baseline Mean (Std)		End of Treatment Mean (Std)		Change Mean (Std)	
	Pancrease MT	Placebo	Pancrease MT	Placebo	Pancrease MT	Placebo
Female	88.65 (5.9) (n=11)	92.08 (4.7) (n=7)	87.60 (6.6) (n=11)	**74.83 (13.7)** (n=7)	1.05 (5.4) (n=11)	**17.25 (13.2)** (n=7)
Male	87.7 (4.2) (n=9)	89.67 (4.4) (n=13)	85.76 (9.9) (n=9)	**46.43 (24.2)** (n=13)	1.94 (6.7) (n=9)	**43.24 (22.3)** (n=13)

As it is noted in bold in Table 3, female subjects in the Placebo arm had a much smaller decrease in their COA-fat than their male counterparts. The differences in treatment group means were statistically significant with each subpopulation ($p<0.001$ for males and $p=0.006$ for females).

Analysis by age category for adults and children/adolescent showed a non-significant treatment-by-age category interaction (p=0.5). The treatment effect within each age category was, however, statistically significant. ($p < 0.001$ for adults and $p < 0.02$ for children/adolescents). Table 4 shows these results.

Table 4: Analysis of COA-fat by Age Category - Mean (Std)

Age Category	Baseline Mean (Std)		End of Treatment Mean (Std)		Change Mean (Std)	
	Pancrease MT	Placebo	Pancrease MT	Placebo	Pancrease MT	Placebo
Adults (>=18 years)	87.7 (5.4) (n=14)	89.7 (4.5) (n=12)	86.6 (9.4) (n=14)	51.5 (25.5) (n=12)	1.2 (5.9) (n=14)	38.2 (24.4) (n=12)
Children/Adolescent (<18 years)	89.1 (4.4) (n=6)	91.7 (4.6) (n=8)	87.1 (4.5) (n=6)	63.6 (23.8) (n=8)	2.0 (6.4) (n=6)	28.1 (20.8) (n=8)

Analysis by site showed a borderline statistically significant treatment-by-center interaction (p=0.1). Since the majority of the centers had less than 5 subjects, we only report the mean change for sites with 5 or more subjects. Table 5 shows these results.

Table 5: Analysis of COA-Fat Change from Baseline by Sites with 5 or More Subjects - Mean ± Std

Site ID	Panrease MT	Placebo
001003 (n=5)	-2.5 ± 0.6 (n=2)	24.5 ± 23.3 (n=3)
001013 (n=8)	2.5 ± 7.0 (n=3)	36.00 ± 23.6 (n=5)
001017 (n=9)	2.9 ± 6.7 (n=6)	19.0 ± 19.6 (n=3)

One center (011001) was from Canada, the rest were from the US. The site in Canada had 2 subjects; both subjects were in the placebo arm.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

No major issues were observed in the review of this NDA. However, when the analyses were performed by gender sub-population, the female subjects in the Placebo arm had a much smaller decrease in their COA-fat than their male counterparts; however both gender subgroups indicate a statistically significant treatment effect.

5.2 Conclusions and Recommendations

From the statistical perspective, the data from Study PNCRLPCYS3001) indicate that Pancrease MT is statistically superior to Placebo with regard to COA-fat and COA-protein endpoints and support the efficacy of this drug in adult and children/adolescent subjects with CF-dependent exocrine pancreatic insufficiency.

Appendix

Table 1: Summary of Subject Disposition

	PANCREASE MT	Placebo	Not randomized	Total
	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

Table 2: Summary of Demographic and Baseline Characteristics

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

Source: Sponsor's Submission – Table 4 Demographic Characteristics – ITT Population, Page 38 of 508 , Study Report

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

---

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

/s/

SHAHLA S FARR
03/01/2010

MICHAEL E WELCH
03/01/2010
Concur with review.