SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	PANCREASE® MT
Name of Active Ingredient(s)	pancrelipase

Protocol No.: PNCRLPCYS3001

Title of Study: A randomized double-blind (withdrawal) Phase 3 study to evaluation the efficacy and tolerability of PANCREASE® MT capsules compared with placebo in the treatment of subjects with cystic fibrosis-dependent exocrine pancreatic insufficiency

Coordinating Investigator: Bruce C. Trapnell, MD – Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; (multicenter study)

Publication (Reference): None

Study Period: 17 July 2008 through 6 February 2009

Phase of Development: Phase 3

Objectives: The primary objective of the study was to evaluate the efficacy of PANCREASE MT delayed-release capsules (MT10.5 or MT21) on the quantitative change in fat absorption in adult and children/adolescent subjects with cystic fibrosis who had clinical symptoms of exocrine pancreatic insufficiency. Overall safety was to be assessed.

The key secondary objective of the study was to evaluate the efficacy of PANCREASE MT delayed-release capsules on the quantitative change in protein (nitrogen) absorption in adult and children/adolescent subjects with cystic fibrosis who had clinical symptoms of exocrine pancreatic insufficiency (EPI). Additional secondary objectives of this study included the evaluation of improvement in clinical signs and symptoms of exocrine pancreatic insufficiency in children/adolescent and adult subjects with cystic fibrosis who had clinical symptoms of exocrine pancreatic insufficiency (nausea, vomiting, bloating, diarrhea, greasy stools, and abdominal pain).

Methods: 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. 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. A Data Safety Monitoring Committee, external to the

Sponsor, was established to monitor data from this study on an ongoing basis to ensure the continuing safety of the subjects enrolled.

Number of Subjects (planned and analyzed): 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; 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. All 40 subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Adults ≥18 to 60 years of age or children/adolescents 7 to <18 years of age; of both sexes; with a diagnosis of CF confirmed by genotype analysis or sweat chloride results (>60 mmol/L); who required PERT to control clinical symptoms of EPI and who had a history of steatorrhea; and who were medically stable on the basis of the physical examination, medical history, and vital signs performed at screening.

Test Product, Dose and Mode of Administration, Batch No.: PANCREASE MT capsules, administered orally, PANCREASE MT 10.5 capsules (Lot number VS 8308-00-A-E) and PANCREASE MT 21 capsules (Lot number VS 8310-00-A-E).

Reference Therapy, Dose and Mode of Administration, Batch No.: PANCREASE MT 10.5 matching placebo capsules (Lot number VS 8309-00-P-E) and PANCREASE MT 21 placebo capsules (Lot number VS 8311-00-P-E)

Duration of Treatment: During the open-label phase, subjects were administered PANCREASE MT 10.5 or MT 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.

Criteria for Evaluation: Efficacy evaluations included the change in percent COA-fat; change in percent COA-protein (nitrogen); assessment of stool; Clinical Global Impression-Severity of illness (CGI-S); Clinical Global Impression-Change (CGI-C); Global Assessment of Change (GAC); and signs and symptoms of EPI during the double-blind phase. Safety assessments included the incidence and severity of reported adverse events, clinical laboratory tests, vital sign measurements, and physical examinations.

Statistical Methods: Assuming the early withdrawal rate in this study was similar to an earlier study (20-101), it was 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. Assuming an early withdrawal rate of 10%, approximately 40 subjects (i.e., 20 subjects per treatment group) were to be randomized into the study. 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 Analysis Set to support the results from the ITT Analysis Set. The ITT Analysis Set included all subjects who were randomly assigned into the double-blind (withdrawal) phase of the study and the Per-protocol 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). For this study, the Completers Analysis Set was identical to the ITT Analysis and is not presented.

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.

RESULTS:

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. All 40 subjects completed the study.

The majority of the subjects in the study were male (55%), ≥18 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.

EFFICACY RESULTS: At the end of the double-blind withdrawal phase, subjects in the PANCREASE MT group had a 1.5% decrease in mean percent COA-fat, compared with subjects in the placebo group, who had a 34.1% decrease in mean percent COA-fat. This difference in the primary efficacy endpoint between the PANCREASE MT group and the placebo group was highly statistically significant ($p<0.001$), favoring PANCREASE MT. Consistent treatment effects were seen across the age subgroups in percent COA-fat, illustrating that PANCREASE MT works well in both children/adolescents and adults. In addition, subjects administered PANCREASE MT had a 1.3% increase in mean percent COA-protein (nitrogen), compared with subjects administered placebo, who had a 26.5% decrease in mean percent COA-protein (nitrogen). The between-group difference in this key secondary efficacy endpoint was also highly statistically significant ($p<0.001$), favoring PANCREASE MT. Consistent with a decrease in the coefficient of fat and protein absorption, the incidence of clinical signs and symptoms of EPI (abdominal pain, bloating, diarrhea, and greasy stools) was higher in the placebo group (55%) than in subjects receiving PANCREASE MT (20%).

Results of the other secondary endpoints of CGI-S, CGI-C, and GAC at the end of the double-blind phase were consistent with the primary efficacy endpoint: in the CGI-S assessment, more PANCREASE MT subjects were assessed as "normal" (85%) than placebo subjects (55%); in the CGI-C, the majority of PANCREASE MT subjects (80%) exhibited no change in disease state or were improved (15%) compared with placebo subjects, who exhibited no change in disease state (35%) or were worse (60%); in the GAC, PANCREASE MT subjects were the same (35%), better (45%), or excellent (20%), while placebo subjects were worse (35%), the same (55%), or better (10%) at the end of the study.

SAFETY RESULTS: No subjects died during the study, and there were no serious adverse events reported during any phase of the study. One subject experienced an adverse event leading to study discontinuation during open-label PANCREASE MT administration; this subject was not randomized into the double-blind phase. No subjects discontinued from the study due to an adverse event during the double-blind phase of the study.

The 38% incidence of treatment-emergent adverse events reported during the open-label phase increased in subjects receiving placebo during the double-blind phase (60%) and remained relatively constant in subjects receiving PANCREASE MT (40%). The most common events were gastrointestinal disorders, including abdominal pain, diarrhea, flatulence, and abnormal feces, and all events were mild or moderate in severity. The majority of treatment-related events were gastrointestinal disorders, although fatigue, asthenia, and decreased appetite were assessed by the investigator as related to study drug administration. Subgroup analysis revealed that the incidence of adverse events in children/adolescents was similar between the 2 treatment groups, but more adults receiving placebo reported adverse events compared with adults receiving PANCREASE MT. The majority of events in both age groups were gastrointestinal disorders. The incidence of adverse events in females was similar between the 2 treatment groups, but more males receiving placebo reported adverse events compared with males receiving PANCREASE MT.

Minor changes in laboratory values and vital sign measurements observed in subjects from screening through the end of the study, were not considered clinically meaningful by the Medical Monitor.

Administration of PANCREASE MT proved to be safe in this population of cystic fibrosis subjects with EPI. No new safety concerns were identified in subjects administered PANCREASE MT in this study.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

The efficacy of PANCREASE MT was demonstrated by a statistically and clinically significant difference ($p<0.001$) in both the primary (quantitative change in fat absorption) and key secondary (quantitative change in protein [nitrogen] absorption) efficacy parameters. Consistent with a decrease in the coefficient of fat and protein (nitrogen) absorption, the incidence of clinical signs and symptoms of EPI (abdominal pain, bloating, diarrhea, and greasy stools) was higher in the placebo group than in subjects receiving PANCREASE MT.

Administration of PANCREASE MT was safe in this population of children/adolescent and adult subjects with cystic fibrosis, and no new safety concerns were identified.

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