SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development
Name of Finished Product	PANCREASE® MT
Name of Active Ingredient(s)	Pancrelipase microtablets

Protocol No.: PNCRLP-CYS-1001; Phase 1

Title of Study: A Single-Dose, Open-Label, Randomized, Crossover Study to Evaluate Intraduodenal Enzyme Delivery of PANCREASE® MT in Subjects with Severe Exocrine Pancreatic Insufficiency.

Principal Investigator: Phillip, P. Toskes, M.D. – University of Florida, Gainesville, Florida, USA

Publication: This study has not been published.

Study Period: 22 July 2008 to 23 January 2009

Phase of Development: Phase 1

Objectives: The primary objective of this study was to evaluate intraduodenal enzyme (lipase, amylase, and protease) delivery of a single dose of PANCREASE MT capsules in subjects with severe pancreatic insufficiency with steatorrhea due to chronic pancreatitis or exocrine pancreatic insufficiency (EPI) of other etiology (severe EPI). The secondary objective was to evaluate the safety and tolerability of a single dose of PANCREASE MT capsules in subjects with severe EPI.

Methods: This was a single-dose, open-label, randomized, 2-way crossover study of PANCREASE MT capsules in subjects, 18 to 85 years of age, inclusive, who had severe EPI. All subjects were randomly assigned to 1 of 2 treatment sequences in each period. Treatment A consisted of a high-fat liquid meal and treatment B consisted of 3 PANCREASE MT 21 capsules administered simultaneously with a high-fat liquid meal. The high-fat meal was the same as used in Treatment A. The study consisted of a screening phase (within 21 days before the first study treatment administration); an open label treatment phase consisting of 2 treatment periods separated by a 2-day washout; and an end-of-study evaluation either upon successful completion of the sample collection in Period 2 or upon study withdrawal. The subject was required to stay an additional night in the study center for observation after the completion of the sample collection at the end of the study. In each treatment period, following an overnight fast of at least 10 hours, subjects were intubated with a Dreiling-like tube for the perfusion of carbon-14 (^{14}C) polyethylene glycol (PEG)/saline solution and collection of gastric and duodenal fluid samples. A 30-minute washout duodenal fluid sample followed by a 30-minute baseline duodenal fluid sample was collected. After collection of the baseline sample, the appropriate study treatment according to the randomization schedule was administered. Study treatment was swallowed by mouth. No additional food was allowed until the completion of the 2-hour postdose evaluation in each period. 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.

Adverse events were monitored throughout the study from the time a consent form was signed until discharge from the study (end-of-study evaluation after Period 2 or early withdrawal). Subjects were directed to voluntarily report any serious adverse events that occurred up to 30 days following discharge from the study.

Number of Subjects (planned and analyzed): Approximately 20 subjects were planned to be enrolled, 13 subjects were enrolled and randomized and 12 completed the study. The pharmacokinetic and safety analyses were done for all 12 subjects.

Diagnosis and Main Criteria for Inclusion: Man or woman between 18 and 85 years of age, inclusive, who had severe pancreatic insufficiency with steatorrhea due to chronic pancreatitis, or EPI of other etiology (severe EPI).

Test Product, Dose and Mode of Administration, Batch No.: Three PANCREASE MT 21 capsules (total of 63,000 USP units of lipase) were administered by mouth simultaneously with a high-fat liquid meal and the batch number was: VS 8310-00-A-E.

Reference Therapy, Dose and Mode of Administration, Batch No.: None

Duration of Treatment: Subjects received either a high-fat liquid meal or 3 PANCREASE MT 21 capsules, which contain a total of up to 63,000 USP units of lipase, administered simultaneously with a high-fat liquid meal on Day 1, which was ingested over 20 minutes or less. There was a 2-day washout between administrations of the study treatment.

Criteria for Evaluation: The primary objective was to evaluate intraduodenal enzyme (lipase, amylase, and protease) delivery and the secondary objective was to evaluate safety.

Pharmacokinetics (enzyme activity): A pretreatment baseline duodenal fluid sample was collected after a successful intubation. Post-treatment duodenal fluid samples were drawn continuously for 2 hours and pooled every 15 minutes. Gastric fluid was collected at the end of each study period. Samples were analyzed for volume, pH, and ^{14}C-radioactivity as well as lipase, amylase, and protease activity by a validated assay.

Safety: Safety and tolerability were evaluated throughout the study. Safety assessments consisted of physical examinations and vital sign assessments as well as the monitoring of adverse events during the course of the study. All adverse events occurring through the end-of-study evaluations and self-reported up to 30 days following discharge from the study were reported by the subject and were documented on the CRF and the source documents. The total amount of blood drawn for clinical laboratory tests was approximately 20 mL.

Statistical Methods:

Sample Size Determination: The number of subjects selected for this study was not based on formal statistical consideration. Based on FDA "Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs" (April, 2006), a sample size of 12 subjects was selected for this study. A sample size of 12 subjects to complete the study was expected to be sufficient to characterize the preliminary safety and enzyme activity in subjects with severe EPI. To account for early withdrawal, approximately 20 subjects were to be enrolled to ensure that 12 subjects completed the study. Once 12 subjects completed the study, enrollment was to end.

Pharmacokinetics (enzyme activity): Treatment A served as time-matched baseline for Treatment B. Parameters of gastric and duodenal sample characteristics (volume, pH, ^{14}C radioactivity, and lipase, amylase, and protease activity) were listed and summarized with descriptive statistics. There were two data sets, the Evaluable Data Set (all subjects who completed at least one treatment with complete or extrapolatable intraduodenal enzyme sample collection), and the Analysis Data Set (all subjects who completed the study). A subject was considered to have completed the study if the subject received both treatments, completed all assessments as planned, had not met withdrawal criteria, and completed the end of study procedures.

Parameters of gastric and duodenal sample characteristics (volume, pH, ^{14}C-radioactivity, and lipase, amylase, and protease activity) were listed and summarized with descriptive statistics. The activity-time profiles of duodenal enzymes (lipase, amylase, and protease) and pH were graphed.

Safety: Safety evaluations include adverse event monitoring, clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital signs measurements, and physical examinations. All subjects who received at least one study treatment were included in the safety analysis.

RESULTS:

A total of 13 subjects were enrolled, and 12 completed the study. One subject (100113) withdrew consent and did not complete the study.

Study Completion/Withdrawal Information
(Safety Analysis Set in Study JJPRD PANCREASE-CYS1001)

Subject Completed Treatment/Trial Reason For Withdrawal/Termination	A[a]/B[bc] (N=6) n (%)	B/A[d] (N=7) n (%)	Total (N=13) n (%)
Completed	6 (100)	6 (86)	12 (92)
Withdrawn	0	1 (14)	1 (8)
Withdrawal of consent	0	1 (14)	1 (8)

Note: Percentages calculated with the number of subjects in each group as denominator.
[a]Treatment A: High-fat liquid meal
[b]Treatment B: 3 PANCREASE MT 21 capsules administered simultaneously with a high-fat liquid meal
[c]A/B = Treatment A/Treatment B
[d]B/A = Treatment B/Treatment A

Nine of the subjects were male, and most (11 subjects) were white. The 2 treatment sequences were generally well balanced with respect to demographic and baseline characteristics, although the percentage of male subjects was higher in the B/A treatment sequence (86%) than in the A/B treatment sequence (50%).

PHARMACOKINETIC RESULTS: Twelve subjects completed the study and were evaluable for both Treatments A and B. All 12 subjects were included in the pharmacokinetic data analysis set. Among those 12 subjects, a total of 6 samples of various matrices were without analytical results. Mean duodenal pH during the entire perfusion ranged from 4.9 to 6.3 for Treatment A (CV less than 33%) within each collection interval. Duodenal pH during perfusion for Treatment B was comparable, with mean values ranging from 5.2 to 6.3 (CV less than 32%). For both treatments, pH measurement immediately after either treatment was elevated compared with the pre-treatment periods and gradually returned to baseline values. Variability seemed to be relatively high during the washout and baseline periods when perfusion was first initiated, but decreased immediately with the initiation of either treatment and remained relatively low throughout the first hour post-treatment. Towards the second hour of post-treatment perfusion, variability tended to increase gradually to a comparable level to pre-treatment. Mean gastric pH at the end of the study was 4.0 for Treatment A (range 1.9 to 6.3), and 4.4 for Treatment B (range 1.9 to 6.2). There were 3 incidences each from either treatment that recorded a gastric pH greater than or equal to 5.5.

The within-treatment, baseline-corrected enzyme activities between two crossover treatments were not clearly differentiable. The conversion factor between different analytical methods for lipase activity was determined to be 2.03. Mean relative local bioavailability of lipase in PANCREASE MT was 19% with a CV of 156% after taking into consideration the conversion factor and utilizing the double correction method. Due to the lack of a conversion factor for the other 2 enzyme assays, relative bioavailability could not be calculated. Residual gastric enzyme activities were negligible after either treatment. Median within-treatment baseline-adjusted duodenal enzyme activities were slightly higher for Treatment B. However the total drug-related duodenal enzyme activities were relatively low when compared to the administered dose.

SAFETY RESULTS: There were no deaths, serious adverse events, or discontinuation due to adverse events reported in this study. There was 1 adverse event reported during the study, which the investigator did not attribute to study medication. Subject 100111 reported a mild adverse event of increased body temperature during period 2, following administration of a high-fat liquid meal and 2 days after administration of PANCREASE MT.

There were no clinically relevant changes in laboratory tests, or vital signs.

CONCLUSIONS:

- Mean relative duodenal bioavailability of lipase in PANCREASE MT was 19% and highly variable with a CV of 156%.
- However, duodenal enzyme recovery results from this current bioactivity study may not reflect demonstrated clinical efficacy and/or patient experience from long history of use.
- PANCREASE MT 21 is well tolerated when administered as 3 MT 21 capsules, containing a total of 63,000 USP units of lipase by the subjects with severe EPI enrolled in this study.

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