SYNOPSIS

Name of Sponsor/Company McNeil Pediatrics Division of McNeil-PPC, Inc. ***Name of Finished Product:*** Pancrease® MT ***Name of Active Ingredient:*** Pancrelipase microtablets ***Protocol no.:*** CR002665	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

Title of Study: A Phase II, Randomized, Investigator-Blinded, Parallel-Group Pilot Study Evaluating the Safety, Palatability and Efficacy of Four Doses of Pancrelipase Microtablets in the Treatment of Infants and Toddlers with Cystic Fibrosis-Related Pancreatic Insufficiency and Fat Malabsorption.

Investigators: The five investigators are listed in Section 4.

Study Centers: The five investigative sites are listed in Section 4.

Publication (reference): Behm MO, Lennartz P, Mulberg AE. Investigation on the behavior of pancrelipase microtablets (Pancrease MT), enteric-coated, dispersed in formula. Clin Pharmacol Ther 2006;79(2):P70.

Study Period: ***Phase of Development:*** II
Date of first enrollment: July 15, 2005
Date of last completed: February 13, 2006

Objectives: The objectives of this study were to evaluate preliminary safety, palatability and efficacy of pancrelipase microtablets to improve steatorrhea in infants and toddlers with cystic fibrosis (CF).

Methodology: This study was a phase II, randomized, investigator-blinded, parallel-group, pilot study that enrolled 18 subjects aged six to 30 months who had CF with pancreatic insufficiency and were stable on current enzyme therapy. As part of Visit 1 (Day 1), parents/guardians were instructed to administer pancrelipase microtablets 500 USP units lipase/kg/meal for five full days (120 hours) on an out-patient basis. Stools were collected during the last 72 hours of the first period (baseline period) during which a defined diet was administered to the infant/toddler. At home or during Visit 2 for randomization (Day 6), a ^{13}C-mixed triglyceride (MTG) substrate breath test was performed. Subsequently, subjects were randomly assigned to one of four treatment groups in a 1:1:1:1 ratio as follows: pancrelipase microtablets at 500 units lipase/kg/meal, 1000 units lipase/kg/meal, 1500 units lipase/kg/meal, or 2000 units lipase/kg/meal. The pancrelipase microtablet dose was dependent upon the amount of units of lipase/kg weight as the critical dosing criterion. Each bottle contained the meal specific dose required for each dose group. At that time, the parents/guardians were instructed to administer the appropriate dose for five full days (120 hours) on an outpatient basis. Stool for quantification of fecal fat and nitrogen was collected and analyzed during the last 72 hours of this randomization period (end of study period) on the defined diet. Dietary intake for the duration of the stool collection was

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recorded for the calculation of the coefficient of absorption (COA) of fat. A repeat MTG substrate breath test was performed at home or at the study center during Visit 3 (Day 11). Assessments of severity of illness, improvement of CF symptoms from baseline, effectiveness and palatability were performed by the investigator and/or parents/guardians at specified visits during the study. The duration of the study was 11 days and consisted of Visit 1 (Day 1), run-in period (Days 1-6), Visit 2 (Day 6), randomized period (Days 6-11) and ended with Visit 3 (Day 11).

Number of Subjects (planned and analyzed): Approximately 20 subjects were planned to be enrolled, 18 subjects were enrolled, 17 were randomized and 16 completed the study.

Diagnosis and Main Criteria for Inclusion: Infants and toddlers ages six to 30 months who had a history of CF-related pancreatic insufficiency with a documented history of abnormal coefficient of fecal fat absorption.

Test Product, Dose and Mode of Administration, Batch Number:
The following four study treatments were administered by mouth on a spoon with applesauce, banana, or formula and were from batch number Vs 5292-00-a-e.

1. Pancrelipase microtablets 500 USP units lipase/kg/meal
2. Pancrelipase microtablets 1000 USP units lipase/kg/meal
3. Pancrelipase microtablets 1500 USP units lipase/kg/meal
4. Pancrelipase microtablets 2000 USP units lipase/kg/meal

Duration of Treatment: 11 Days (run-in period during Days 1-6, randomized period during Days 6-11).

Reference Therapy, Dose and Mode of Administration, Batch Number: None

Criteria for Evaluation:
Efficacy: The primary endpoints were:

- The change in the COA of fat measured from Visit 2 (Randomization) to the Visit 3 (End of Study)
- Daily palatability assessed using a 4-point scale
- Percentage of carbon dioxide (CO_2) expired (cumulative $\%^{13}C$) by an MTG substrate breath test as a surrogate marker of lipase activity and the pharmacodynamic effect of pancreatic enzyme therapy

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The secondary endpoints for this study were:

- Clinical Global Impression (CGI) of Severity of Illness subscale (CGI-S)
- Investigator Assessment of Improvement (using CGI-C)
- Parental Assessment of Improvement (using CGI-C)
- Weight loss/gain during the study period
- Global Assessment of Effectiveness (GAE)
- Dose of pancreatic enzymes assessed per day and weight
- Daily calories, fat and protein intake as measured by 24-hour food records during the run-in and randomization treatment periods
- Correlation between COA of fat, and mean units lipase/meal, fat intake, and weight
- Correlation between COA of protein, and mean units protease/meal, protein intake, and weight
- The change in COA of protein (nitrogen) measured from the baseline period to the end of the study period

Safety: Safety assessments consisted of physical examinations and vital sign assessments as well as the monitoring of adverse events during the course of the study.

Statistical Methods: Most statistical analyses carried out were descriptive in nature. Continuous variables were summarized using number of observations, mean, standard deviation, median, and range (minimum, maximum). Categorical variables were summarized using frequencies and percentages. Demographic and baseline characteristics were summarized descriptively. Descriptive statistics were also used to summarize all efficacy parameters by treatment group. For the safety analyses, the number and percent of subjects with specific adverse events were tabulated by treatment pre- and post-randomization, using MedDRA system organ class and preferred term.

Efficacy Results:

Table 1-1 and Table 1-2 present a summary of the primary and secondary efficacy results. There were three primary efficacy endpoints: the change in COA of fat measured from the randomization to the end of study, daily palatability assessed using a 4-point scale, and percentage of CO_2 expired (cumulative $\%^{13}C$) by an MTG substrate breath test as a surrogate marker of lipase activity and the pharmacodynamic effect of pancreatic enzyme therapy. No clinically important changes were found in mean COA of fat from randomization to the end of study within any treatment group. Subjects maintained a COA of fat close to 90% and there were no clinically important differences among treatment groups from randomization to the end of study, which suggests that pancrelipase microtablets were equally effective at all doses for the treatment of steatorrhea.

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Palatability of all doses of study medication was good. The mean overall palatability scores were 2.2 for the run-in period and 2.1 for the randomized period. Mean scores were ≥2.0 during the randomized period for all but the highest dosage group, for which the mean score was 1.6. For subjects with adequate breath samples, improved lypolysis was demonstrated with increasing dosage. The mean percent difference in cumulative $\%^{13}C$ from randomization to the end of study was -1.77%, -1.60%, 15.35%. and 125.32% in the 500 units lipase/kg/meal, 1000 units lipase/kg/meal, 1500 units lipase/kg/meal, and 2000 units lipase/kg/meal groups, respectively.

For the secondary endpoints of investigator assessment of improvement, parental assessment of improvement, and global assessment of effectiveness, there were no clinically important changes in mean scores within any treatment group from randomization to end of study. There was a suggestion of a trend toward greater improvement with increasing dosage. There were no clinically important changes in mean CGI-S score within any treatment group and there were no clinically important differences among treatments groups in the change in mean CGI-S score from randomization to the end of study.

Subjects maintained their weight during the study. There were no clinically important changes in mean weight within any treatment group and there were no clinically important differences among treatments groups in change in mean weight from screening to randomization, from randomization to the end of study, or from screening to the end of study. There were no clinically important differences in the mean dose of pancreatic enzymes administered per day throughout the randomized period across time in any of the treatment groups. Average daily intake of calories, fat and protein was also comparable across time and among treatment groups. There were no clinically important changes in mean COA of protein (nitrogen) within or among treatment groups.

A linear regression analysis was performed using COA of fat or COA of protein as response variables with weight, dose, and fat or protein intake as independent variables in the models. A marginally strong but significant partial correlation coefficient (ρ) observed between COA of fat and weight (ρ=0.5354, p-value=0.0485) and between COA of protein and protein intake (ρ=0.6424, p-value=0.0132).

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Table 1-1. Summary of Efficacy Results

Measure	Pancrease MT Treatment Group			
	500 units lipase/kg/meal N=4	1000 units lipase/kg/meal N=4	1500 units lipase/kg/meal N=4	2000 units lipase/kg/meal N=4
Primary Endpoints, Mean (SD)				
COA (%) of Fat, Δ[a] from Visit 2	-1.74 (2.529)	1.14 (2.802)	-1.16 (2.584)	-2.14 (3.227)
Palatability[b], Overall	2.8 (0.50)	2.0 (1.13)	2.0 (0.82)	1.6 (1.60)
Cumulative ^{13}C % difference[c] from Visit 2	-1.77 (29.65)[f]	-1.60 (82.93)[f]	15.35 (77.45)[f]	125.32 (86.41)[f]
Secondary Endpoints, Mean (SD)				
CGI-S, Δ[a] from Visit 2	0.3 (0.50)	0.0 (0.00)	0.0 (0.00)	0.3 (0.50)
Investigator Assessment of Improvement, Δ[a] from Visit 2	0.25 (0.957)	-0.25 (0.500)	-0.75 (0.957)	-1.00 (1.414)
Parental Assessment of Improvement, Δ[a] from Visit 2	0.00 (0.816)	0.00 (0.000)	-0.75 (0.957)	-1.25 (2.500)
Weight Loss/Gain During Study Period, Δ[d] from Visit 1	0.05 (0.129)	0.30 (0.408)	-0.05 (0.129)	0.13 (0.350)
GAE, Δ[a] from Visit 2	-0.3 (1.26)	0.0 (0.82)	0.5 (1.00)	0.8 (0.50)
Dose (lipase/kg/day), Overall[e]	1833 (204.12)	3833 (1160.70)[g]	6313 (1390.07)	7917 (1449.78)
Daily Calories (Cal), Overall[e]	1187 (327.26)	890.5 (311.95)[g]	878.1 (218.07)	847.1 (222.52)
Daily Fat Intake (g), Overall[e]	39.4 (9.42)	35.1 (10.50)[g]	34.0 (10.86)	28.9 (7.69)
Ratio of Daily Fat Intake (g)/Weight (kg), Overall[e]	3.5 (0.80)	3.8 (1.75)[g]	4.3 (2.16)	2.8 (0.70)
Daily Protein Intake (g), Overall[e]	31.4 (7.47)	25.2 (11.71)[g]	23.7 (9.95)	24.8 (4.71)
Ratio of Daily Protein Intake (g)/Weight (kg), Overall[e]	2.8 (0.59)	2.7 (1.31)[g]	2.7 (0.46)	2.3 (0.13)
COA(%) of Protein, Δ[a] from Visit 2	-6.06 (2.926)	3.15 (2.117)	3.37 (6.334)	-1.72 (7.150)

a: Value at Visit 3 - Value at Visit 2
b: Palatability Scores: 0=poor; 1=fair; 2=good; 3=excellent
c: [(Value at Visit 3 – Value at Visit 2)/Value at Visit 2]x100 for subjects with adequate breath samples
d: Value at Visit 3 - Value at Visit 1
e: Overall intake is the mean of daily intake for all days in each study period.
f: N=3 for the 500 units, 1000 units, 1500 units, and 2000 units lipase/kg/meal groups
g: N=5 for the 1000 units lipase/kg/meal group

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Table 1-2. Summary of Efficacy Results - Partial Correlation Coefficients for COA of Fat and COA of Protein

	Partial Correlation Coefficients[a]		
	Mean Units lipase/kg/meal or Protease/kg/meal	Weight	Fat/Protein Intake
COA of Fat	0.0878	0.5354[b]	0.4353
COA of Protein	0.2295	-0.1056	0.6424[c]

a: Based on the linear regression, COA=mean units/kg/meal + weight + fat or protein intake
b: statistically significant, p=0.0485
c: statistically significant, p=0.0132

Safety Results:

The study medication at dosages of 500 to 2000 USP units lipase/kg/meal was well tolerated. The intensity and nature of adverse events were similar for all doses of pancrelipase microtablets. There were no deaths during the study. No serious adverse events were reported, and no subjects withdrew from the study due to adverse events. Adverse events were reported for three subjects (16.7%) during the open-label run-in period. Adverse events were reported for four subjects during the randomized period; one (25.0%) in the 500 units lipase/kg/meal group, one (20.0%) in the 1000 units lipase/kg/meal group, and two (50.0%) in the 2000 units lipase/kg/meal group. Gastrointestinal disorders were the most frequently reported adverse events, reported for two (11.1%) subjects during the open-label period and three subjects during the randomized period; one (25%) in the 500 units lipase/kg/meal group, one (20%) in the 1000 units lipase/kg/meal group, and one (25%) in the 2000 units lipase/kg/meal group. This is consistent with the known gastrointestinal effects of pancrelipase. Drug-related adverse events were reported for two subjects in the open-label run-in period, and three subjects during the randomized period. There were no clinically important differences among treatment groups with respect to changes during the randomized period in vital signs, respiration, temperature, and length.

Conclusions:

- No clinically important changes were found in mean coefficient of absorption (COA) of fat from randomization to the end of study within or among treatment groups. Subjects maintained a COA of fat close to 90% which suggests that pancrelipase microtablets were equally effective at all doses.

- Palatability of all doses of study medication was good. The mean overall palatability scores were 2.2 for the run-in period and 2.1 for the randomized period. Mean scores were ≥2.0 during the randomized period for all but the highest dosage group, for which the mean score was 1.6.

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- For subjects with adequate breath samples, improved lypolysis was demonstrated with increasing dosage. The mean percent difference in cumulative $\%^{13}C$ from randomization to the end of study was -1.77%, -1.60%, 15.35%, and 125.32% in the 500 units lipase/kg/meal, 1000 units lipase/kg/meal, 1500 units lipase/kg/meal, and 2000 units lipase/kg/meal groups, respectively.

- A marginally strong but significant partial correlation coefficient (ρ) was observed between COA of fat and weight (ρ=0.5354, p=0.0485) and between COA of protein and protein intake (ρ=0.6424, p=0.0132), based on a linear regression model with weight, dose, and fat or protein intake as covariates.

- For the secondary endpoints of investigator assessment of improvement, parental assessment of improvement, and global assessment of effectiveness, there were no clinically important changes from randomization to the end of study in mean scores within any treatment group. Comparison of the changes in mean scores among treatment groups suggest a trend toward greater improvement with increasing dosage.

- Subjects maintained their weight during the study. There were no clinically important differences in the mean dose of pancreatic enzymes administered per day across time in any of the treatment groups. Average daily intake of calories, fat and protein was also comparable within and among treatment groups. There were no clinically important changes in mean clinical global impression of severity of illness subscale scores and mean COA of protein (nitrogen) within or among treatment groups.

- The study medication at dosages of 500 to 2000 USP units lipase/kg/meal was well tolerated. There were no deaths, serious adverse events, or withdrawals from the study due to adverse events. Adverse events were reported for three subjects in the open-label run-in period, and four subjects in the randomized period. Gastrointestinal disorders were the most frequently reported adverse events. There were no clinically important differences among treatment groups with respect to changes during the randomized period in vital signs, respiration, temperature, and length.

Date of the Report: September 19, 2006

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