SYNOPSIS

Name of Sponsor:
Solvay Pharmaceuticals, Inc

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:
Pancrelipase delayed release capsules

Name of Active Ingredient:
Pancreatin/pancrelipase

Study Title:
A Study to Investigate the Effect of Pancrelipase Delayed Release Capsules on Maldigestion in Patients with Exocrine Pancreatic Insufficiency Due to Chronic Pancreatitis and Pancreatectomy

Investigators:
46 Investigators consented subjects

Study Centers:
46 centers consented subjects in Bulgaria, Poland, Russia, Serbia, Ukraine, and the United States

Publication (Reference):
Not applicable

Study Period: Randomized Double-Blind Period:
04 APR 2007 (first subject first visit) to
18 AUG 2008 (last subject last visit)

Phase of Development:
IIIb

Objectives:
The primary objective was to compare the change in the coefficient of fat absorption (CFA) from baseline (i.e., during placebo run-in period) to the end of double-blind treatment for the pancrelipase delayed release capsules and placebo treatment groups.

The secondary objectives were to investigate the effect of pancrelipase delayed release capsules on the coefficient of nitrogen absorption (CNA), stool fat, stool weight, nutritional parameters (triglycerides, low density lipoprotein [LDL] cholesterol, high density lipoprotein [HDL] cholesterol, retinol-binding proteins, pre-albumin, cholesterol), clinical symptomatology (stool frequency, stool consistency, abdominal pain, flatulence, appetite), quality of life using the SF-36, and body mass index (BMI).

The safety and tolerability objectives were to evaluate the short-term safety of pancrelipase delayed release 12000 capsules and the long-term safety and tolerability of pancrelipase delayed release 24000 unit capsules including vital signs, safety laboratory values, and adverse events (AEs)

Methodology:

The study was a multi-center, double-blind, two-arm parallel-group, randomized, placebo-controlled trial with an open-label, long-term extension. Results from the open-label period will be presented in a separate report.

Number of Subjects (Planned, Consented, Randomized and Analyzed):

Approximately 52 subjects were to be randomized. Enrollment was to continue until at least 46 subjects (23 per treatment group) were evaluable for the analysis of the primary efficacy variable. The estimated screen failure rate is 50%.

A total of 180 subjects consented, 54 subjects were randomized (25 subjects to pancrelipase and 29 subjects to placebo), 54 subjects were analyzed for safety, and 52 subjects were included in the full analysis (FA) sample used for the primary efficacy analysis.

Diagnosis and Main Criteria for Inclusion:

Exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis or pancreatectomy

Test Product, Dose and Mode of Administration, Batch Number:

Pancrelipase delayed release 12000 unit capsules and pancrelipase delayed release 24000 unit capsules administered orally.

Dose during double-blind period: 6 capsules per main meal (3 main meals) plus 3 capsules per snack (2 snacks) using pancrelipase delayed release 12000 unit capsules. Batch numbers: ICN 69990, ICN 70412, ICN 70936.

Dose during open-label period: individualized dosing using pancrelipase delayed release 24000 unit capsules.

Duration of Treatment:

- Run-in treatment period: 5 days of single-blind placebo treatment
- Intervening period: up to 16 days of Investigator-directed treatment with no restrictions on pancreatic supplementation
- Randomized treatment period: 7 days of double-blind, placebo-controlled treatment
- Open-label treatment period: 6 months of open-label treatment with pancrelipase delayed release capsules

Reference Therapy, Dose and Mode of Administration, Batch Number:

Matching placebo capsules were administered during the run-in and randomized periods as follows: 24 placebo capsules per day; 6 capsules per main meal (3 meals) and 3 capsules per snack (2 snacks). Batch numbers: ICN 69989, ICN 70413, ICN 70935.

Criteria for Evaluation

Efficacy:

The primary efficacy parameter was the change in CFA from baseline to the end of double-blind treatment.

Secondary efficacy parameters included comparison of CNA, stool fat, stool weight, nutritional parameters (triglycerides, LDL cholesterol, HDL cholesterol, retinol-binding proteins, pre-albumin, and cholesterol), clinical symptomatology (stool frequency, stool consistency,

abdominal pain, flatulence, and appetite), quality of life using the SF-36, and BMI.

Safety:

The safety and tolerability data collected during this study included vital signs, safety laboratory values, and AEs.

Statistical Methods:

Efficacy:

The primary efficacy analysis was performed on the full analysis (FA) sample, which included all subjects who had at least one dose of study medication and for whom at least one post-baseline efficacy measurement was available.

The primary objective of this trial was to show superior efficacy of pancrelipase delayed release capsules over placebo. The primary efficacy variable was the change in CFA from baseline to the end of the double-blind treatment period.

For the primary efficacy variable, an analysis of covariance (ANCOVA) model was assumed with the treatment group as a fixed factor and the CFA at baseline as a covariate. Any test to compare treatment groups was performed within this model by the respective linear contrasts. The following null-hypothesis was tested ($\mu 0$ and $\mu 1$ denote the treatment group means of the primary efficacy variable in the placebo and pancrelipase delayed release capsules group):

H0: $\mu_0 = \mu_1$ (i.e., placebo and pancrelipase delayed release capsules are equal)

The primary objective is to show superior efficacy of pancrelipase delayed release capsules over placebo at alpha level of 15% two-sided.

All efficacy variables both during the double-blind treatment period and during the open-label extension period were summarized by standard descriptive methods.

Safety:

The safety sample included all subjects who had at least one dose of study medication. The safety sample was used for the analysis of the safety and tolerability data. Treatment-emergent AEs (TEAEs) were summarized by unique treatment (double-blind period: pancrelipase delayed release capsules, placebo; open-label extension period: pancrelipase delayed release capsules). Severity and drug-event relationship of TEAEs were summarized separately.

Laboratory variables, including changes from baseline, were summarized. A frequency table is presented for markedly abnormal values. Shift tables are presented according to the reference ranges (low, normal, or high).

Vital signs, including changes from baseline, were summarized. A frequency table is presented for markedly abnormal values.

All safety variables were summarized.

Summary – Conclusions

This report presents the results collected through the end of the double-blind period of this study. Results from the open-label period, including nutritional parameters, will be presented in a separate report.

Efficacy Results:

- The study met its primary objective and demonstrated a statistically significant and clinically relevant superiority of pancrelipase treatment over placebo on the primary outcome measure of change from baseline CFA. The mean change from baseline CFA was greater in the pancrelipase group (31.93%) compared with the placebo group (8.72%), and the difference was statistically significant (LS mean difference: 21.22%, $p < 0.0001$). Of note, due to the significance of a treatment and baseline CFA interaction term as part of ANCOVA assumption checks, the p-value for the non-parametric ANCOVA test for the difference in treatment groups was used. The results of supportive analyses of the CFA were highly consistent with the results of the primary efficacy analysis.
- Marked improvement was noted in the secondary outcome measure of change from baseline CNA. The mean change from baseline CNA was greater in the pancrelipase group (35.23%) compared with the placebo group (8.85%), with LS mean difference of 20.55% ($p = 0.0002$) (non-parametric ANCOVA, $p = 0.0005$).
- There was a greater decrease in stool fat and stool nitrogen in the pancrelipase group compared with the placebo group. No meaningful difference from baseline was noted for fat intake or nitrogen intake in either treatment group.
- Analyses of clinical symptomatology suggested a beneficial effect of pancrelipase on stool frequency, stool consistency, and flatulence; while abdominal pain appeared to be less affected possibly due to minimal pain at baseline. Diary data were consistent in general with the results of clinical symptomatology evaluations and reflected a beneficial effect of pancrelipase on stool frequency, stool consistency, and flatulence; while abdominal pain and appetite did not show notable improvement.
- No consistent changes or meaningful treatment group differences were noted in the Clinical Global Impression of Disease Symptoms at any study visit. No consistent changes or meaningful treatment group differences were detected in any of the eight domains or summary scores of the SF-36 Health Survey as might be expected in a short duration study.
- Subgroup analyses by baseline CFA indicated that more severe disease (lower baseline CFA) was associated with greater improvements in CFA and CNA. Disease status (chronic pancreatitis or pancreatectomy) did not seem to affect the efficacy of pancrelipase on the CFA. However, pancrelipase treatment produced a larger change from baseline in CNA in subjects who had undergone pancreatectomy compared to subjects with chronic pancreatitis. It is important to note that this observation was most likely due to lower baseline CNA values in the pancreatectomy subgroup. Pancrelipase produced a larger change from baseline in CFA in subjects with concomitant PPI or H2-receptor antagonist use but again, this was most likely due to differences in baseline CFA values. Geographical region (US or Central and Eastern Europe) or history of cholecystectomy (yes or no) did not seem to affect the magnitude of the benefits observed with pancrelipase treatment as measured by the CFA. No subgroup differences by baseline CFA or disease status were noted in the clinical symptomatology or GI diary data.

Safety Results:

- No death was reported in this study. No treatment-emergent SAEs were reported. No

subject terminated from the study due to TEAEs.

- The overall incidence of TEAEs was low, 20.0% in the pancrelipase group and 20.7% in the placebo group. Analysis of AEs did not reveal any TEAEs with a clinically meaningfully greater incidence in the pancrelipase group compared with the placebo group. No cases of hypersensitivity were reported. Treatment-emergent AEs reported in the pancrelipase group during the randomized period included abnormal feces, flatulence, abdominal pain, frequent bowel movements, nasopharyngitis, diabetes mellitus inadequate control, hyperglycemia, and hypoglycemia (one subject each). One subject in each treatment group reported related TEAEs and one subject in the placebo group reported a severe TEAE. Summary of AEs by disease status and baseline CFA revealed that subjects with pancreatectomy and/or with lower baseline CFA had a higher incidence of TEAEs.
- The results of baseline laboratory and vital sign assessments were reflective of this patient population.

Conclusion:

The results of this study provide strong evidence for the efficacy and safety of pancrelipase delayed release 12000 lipase unit capsules in the treatment of pancreatic exocrine insufficiency due to chronic pancreatitis or pancreatectomy. Pancrelipase delayed release 12000 lipase unit capsules, at a dose of six capsules per main meal and three capsules per snack, administered for 7 days were well tolerated in this patient population with the AE profile for pancrelipase similar to placebo. Results from the open-label period will be presented in a separate report.