SYNOPSIS

Name of Sponsor:
Solvay Pharmaceuticals GmbH

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:
SLV339

Name of Active Ingredient:
Recombinant Microbial Lipase

Study Title:
A multi-center, double-blind, parallel-design, randomized, placebo-controlled, dose-ranging study to assess the efficacy and safety of oral recombinant microbial lipase (SLV339) in subjects with pancreatic exocrine insufficiency due to chronic pancreatitis

Investigator(s):
47 Principal Investigators.

Study Center(s):
47 centers in seven countries.

Publication (Reference):
Not applicable.

Study Period:
21 FEB 2008 (first subject first visit) to
05 MAR 2009 (last subject last visit)

Phase of Development:
IIa

Objectives:
The primary objective of this study was to estimate the dose-response curve for short term efficacy and safety of recombinant microbial lipase (SLV339) in subjects with maldigestion of lipids due to pancreatic exocrine insufficiency (PEI) suffering from chronic pancreatitis (CP).

The safety objective was to assess the short term safety and tolerability including vital signs, safety laboratory values including immunogenic testing, stool characteristics and adverse events (AEs). Testing for antidrug-antibody (ADA) reactions was also to be performed.

Methodology:
This descriptive and exploratory dose-ranging study was a multi-center, double-blind, randomized, four-arm, parallel group, placebo-controlled study to estimate the dose-response curve for short term efficacy and safety of oral recombinant microbial lipase SLV339. Eighty subjects were intended to be randomized to four possible treatment groups (20 subjects per group): 150 mg, 300 mg and 600 mg lipase protein/day or matching placebo. The study consisted of a screening period (duration eight to 10 days), a three to five-week run-in period, a seven-day double-blind treatment period and a 30-day safety follow-up.

After the screening visit (Visit 1), the subjects took the last dose of their usual pancreatic

enzyme supplementation on the evening before the start of the run-in period (five days without pancreatic enzyme treatment). Stool collection was performed for three whole days and dietary recording was performed for four whole days (up to and including Visit 2). There was an option to hospitalize subjects for the stool collection and dietary recording periods. The subjects took their usual pancreatic enzyme supplementation during the waiting period whilst CFA analysis was performed (Visits 2 to 3). The subjects were instructed to have three main meals each day, maintaining a daily fat intake of a minimum of 100-120 g/day during the two stool collection periods.

Only subjects with a CFA of < 80% were randomized to one of the three doses (150 mg, 300 mg or 600 mg lipase) of SLV339 or matching placebo for a treatment period of seven days.

Blood samples were taken at Visits 3 and 4, pre-dose and 30 minutes, 1 hour, 2 hours and 4 hours post-dose for the absorption kinetics of SLV339. Serum was taken pre-dose and post-dose for ADA determination. Antidrug IgA was determined in each 24-hour stool at Visits 3 and 4.

Subjects completed the double-blind treatment period at Visit 4 (Day 8). A safety follow-up phone call was done 30 days after Visit 4.

Number of Subjects (Planned, Consented, Randomized and Analyzed):
Planned: 80 subjects (20 subjects to 150 mg/day lipase, 20 subjects to 300 mg/day lipase, 20 subjects to 600 mg/day lipase and 20 subjects to placebo).

Consented: 247 subjects.

Randomized: 56 subjects (14 subjects to 150 mg/day lipase, 13 subjects to 300 mg/day lipase, 15 subjects to 600 mg/day lipase and 14 subjects to placebo). The study was stopped prematurely due to low recruitment.

Analyzed safety: 52 subjects (13 subjects to 150 mg/day lipase, 12 subjects to 300 mg/day lipase, 14 subjects to 600 mg/day lipase and 13 subjects to placebo).

Analyzed Full Analysis (FA) sample: 52 subjects (13 subjects to 150 mg/day lipase, 12 subjects to 300 mg/day lipase, 14 subjects to 600 mg/day lipase and 13 subjects to placebo).

Analyzed FA-CFA sample (all subjects who were in the FA sample who had a non-negative CFA value at baseline): identical to FA sample; no subjects had a negative CFA value at baseline.

Diagnosis and Main Criteria for Inclusion:
Male or female subjects ≥ 18 years old with confirmed PEI due to CP who are clinically stable on a stable daily dose of pancreatic enzyme supplementation for at least 3 months before the start of the study and who had an untreated CFA of < 80% at baseline (Visit 3, Day 1).

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

Recombinant microbial lipase (SLV339) 50 mg capsules: total daily dose 150 mg, 300 mg and 600 mg (three times daily [tid] regimen). Capsules were to be taken orally during the three main meals.

Batch numbers: ICN 70890 and 1060503-810008.

Duration of Treatment:

Seven days.

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

Placebo capsules matching SLV339, taken orally (tid).

Batch numbers: ICN 70891 and 1060432-810009.

Criteria for Evaluation

Efficacy:

Efficacy parameters - CFA, CNA, stool fat, stool fat concentration**,** stool nitrogen, stool weight, nutritional protein and fat intake and clinical symptomatology (stool frequency, stool consistency, abdominal pain and flatulence).

Safety:

Safety parameters - vital signs, physical examination, laboratory and nutritional examinations (triglycerides, cholesterol, low-density-lipoproteins, high-density-lipoproteins, retinol-binding protein, pre-albumin, albumin, transferrin, vitamin E), ADA measurements and AEs.

Statistical Methods:

Efficacy:

Efficacy analyses were performed on the FA-CFA sample, which included all subjects of the Safety sample who had at least one post-baseline assessment of any efficacy measurement and a non-negative CFA value at baseline.

Efficacy parameters were summarized by dose group with standard statistical characteristics including 95% confidence intervals (CIs) for means and percentages. Exploratory dose-response modeling on the following CFA and safety endpoints was conducted:

- Change from baseline to end of treatment (Visit 4) in CFA.
- Response to CFA: increase of CFA from baseline to end of treatment by at least 15% in absolute terms or a CFA at the end of treatment of at least 85%.
- Normalization of CFA: a CFA of at least 85% at the end of treatment.
- Occurrence of at least one treatment-emergent AE (TEAE).

An analysis of covariance model was explored for the change from baseline to end of treatment in CFA, with dose group as a factor and CFA at baseline as a covariate. In addition, a linear regression modeling procedure was carried out to explore the dose-responses relationship between dose and change from baseline in CFA, including baseline CFA as an explanatory variable and testing the significance of a number of key covariates (including dose^2, age and weight); this procedure was also conducted on log dose. Dose-response curves were also investigated for the dichotomous endpoints using non-linear regression techniques on normal, logistic and extreme value distribution functions. All model curves were presented graphically.

Safety:

The Safety sample was used for the analysis of the safety and tolerability data (i.e. all randomized subjects who had at least one dose of study drug).

Treatment-emergent AEs were summarized by unique treatment. Severity and drug-event relationship of TEAEs were summarized separately. Laboratory variables, including changes from baseline, were summarized. A frequency table was presented for markedly abnormal values. Shift tables were presented according to the reference ranges (low, normal or high). Vital signs, including changes from baseline, were summarized. A frequency table was presented for markedly abnormal values.

Summary - Conclusions

Efficacy Results:

- The objective of estimating a dose-response curve for lipase was achieved for the doses studied (150 mg/day, 300 mg/day and 600 mg/day).Evidence was found that in two of the three lipase dose groups (300 mg/day and 600 mg/day) mean change from baseline to end of treatment in CFA was different from that in the placebo group (ANCOVA analysis). A linear regression analysis in the FA-CFA sample of the change from baseline in CFA at end of treatment supported the results of the ANCOVA analysis in providing evidence that there is a linear relationship between dose and response.
- Overall, only 11 of the lipase-treated subjects in the FA sample achieved a CFA of > 80% at the end of treatment (Visit 4): four, two and five subjects in the lipase 150 mg/day, 300 mg/day and 600 mg/day groups, respectively. A slightly higher number of subjects in the lipase 300 mg/day and 600 mg/day groups had a change from baseline in CFA that was ≥ 15% compared with the lipase 150 mg/day and placebo groups at end of treatment.
- A negative mean CNA was observed at baseline and remained negative during treatment as study treatment did not include protease.
- There was no definitive evidence of actual absorption of lipase in subjects treated with lipase 150 mg/day, 300 mg/day or 600 mg/day. Also, there was no definitive evidence of production of anti-lipase antibody in serum from subjects treated with lipase 150 mg/day, 300 mg/day or 600 mg/day, and no subject had a 24-hour stool sample that was confirmed positive for antidrug IgA.
- Analyses of diary data showed an improvement of stool frequency and stool consistency while abdominal pain and flatulence were not noted to improve.

Safety Results:

- Lipase (at doses of 150-600 mg/day) was well tolerated in this study.
- There were no deaths or treatment-emergent SAEs reported in this study, and no subject terminated from the study due to TEAEs.
- The overall incidence of TEAEs was greater in subjects who received lipase 600 mg/day (71.4% of subjects) and lower in subjects who received lipase 300 mg/day (41.7% of subjects) compared with subjects who received lipase 150 mg/day or placebo (61.5% of subjects each).
- There was no marked evidence of a dose-dependent increase in the incidence of TEAEs.
- The most commonly reported TEAEs were abdominal pain and flatulence.
- Nine subjects overall reported related TEAEs and one subject in the lipase 600 mg/day group and one subject in the placebo group reported a severe TEAE.

- No clinically relevant abnormal changes in mean laboratory or vital sign parameters were observed during the study. There were no clinically significant differences between groups in shifts from baseline to endpoint in laboratory parameters.

Conclusion:

- The objective of estimating a dose response curve for lipase was achieved for the doses studied between dose and the change from baseline to end of treatment in CFA. Higher doses other than those studied (150, 300 and 600 mg/day) might be associated with greater change from baseline to end of treatment in mean CFA, but this cannot be established by the present study. However, all of the dose-response model results should be interpreted with caution due to the relatively small sample size.
- There was no definitive evidence of either actual absorption of lipase or production of anti-lipase antibody in subjects treated with lipase.
- Lipase (at doses of 150 mg/day, 300 mg/day and 600 mg/day) was well tolerated in this subject population with the AE profile for lipase similar to placebo in short term treatment.
- There were no unexpected safety results.