SYNOPSIS

Name of Sponsor:
Abbott Seiyaku K.K.

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:
SA-001 Capsule

Name of Active Ingredient:
SA-001

Study Title:
A One-year Open-label Study to Assess the Safety of Oral Long-term Use of SA-001 in Patients with Pancreatic Exocrine Insufficiency Caused by Chronic Pancreatitis or by Pancreatectomy

Investigator(s):
55 Investigators

Study Center(s):
49 Study centers

Publication (Reference):
Not applicable

Study Period:
08 JAN 2008 (first subject first visit) to
24 SEP 2010 (last subject last visit)

Phase of Development:
III

Objectives:
The primary objective of the study is to evaluate the safety of long-term use of SA-001 3.0 g/day (12 capsules/day), flexibly increased or decreased within the range of SA-001 1.5 g/day (6 capsules/day) to SA-001 6.0 g/day (24 capsules/day), which is to be administered orally for 52 weeks to subjects with PEI caused by chronic pancreatitis in the non-compensatory stage or by pancreatectomy.

This safety evaluation is based on vital signs measurement, clinical laboratory evaluation, and adverse event (AE) monitoring.

The secondary objective of the study is to evaluate the efficacy data (nutritional evaluation items) of SA-001 3.0 g/day (12 capsules/day), flexibly increased or decreased within the range of SA-001 1.5 g/day (6 capsules/day) to SA-001 6.0 g/day (24 capsules/day), which is to be administered orally for 52 weeks to subjects with PEI caused by chronic pancreatitis in the non compensatory stage or by pancreatectomy.

Methodology:
This study is a multi-center, unblinded study without concurrent controls, with the objective of evaluating safety and collecting efficacy data of long-term (52 weeks) use of SA-001 Capsule in patients with PEI caused by chronic pancreatitis in the non-compensatory stage or

pancreatectomy.

The current study is a long-term extension of the S245.3.122 study and included subjects who completed the double-blind S245.3.122 study. Subjects were to be treated with 3.0 g/day SA-001 (12 capsules/day), the clinically recommended dose, in three divided doses immediately after meals (1.0 g per dosing; four capsules); the subject's dose could be increased up to 6.0 g/day SA-001 (24 capsules/day) according to their degree of PEI and number or frequency of their meals or snacks per day.

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

Number of subjects planned: 75 subjects

Number of subjects consented: 80 subjects

Number of subjects enrolled: 80 subjects

Number of subjects analyzed: 80 subjects

Safety Sample: 80 Subjects

Full Analysis (FA) Sample: 79 subjects

Number of subjects completed: 58 subjects.

Diagnosis and Main Criteria for Inclusion:

Male or female subjects who completed the double-blind study (S245.3.122) (excluding discontinued subjects) and who signed the informed consent prior to the initiation of the study.

Subjects who were assessed to be inappropriate for continuing long-term use of SA-001 Capsule, at the discretion of the Investigator or the Sub-investigator, because they experienced adverse drug reactions in the double-blind study (S245.3.122) were to be excluded from the S245.3.123 study. Subjects with a known allergy to porcine protein or any component of digestive enzyme preparations were also to be excluded.

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

SA-001 Capsule containing 0.25 g SA-001 pellets; an enteric-coated preparation containing highly concentrated pancreatin (60% weight/weight [w/w]). SA-001 is a mixture of the following highly active pancreatic enzymes:

- Amylase: 8,500 to 16,200 Fédération Internationale Pharmaceutique-unit/gram (FIP-u/g).
- Lipase: 10,000 to 16,000 FIP-u/g.
- Protease: 450 to 1,125 FIP-u/g.

As a standard subjects were to receive an oral daily dose of 3.0 g/day SA-001 (12 capsules/day) of the study medication three time daily. The basic dose was to be 1.0 g/dosing SA-001 (4 capsules/dosing) after a main meal. The minimum daily dose was to be 1.5 g/day SA-001 (6 capsules/day), and the maximum daily dose 6.0 g/day SA-001(24 capsules/day).

Batch number:	0011	Expiry date:	31 MAY 2009
Batch number:	0015	Expiry date:	30 NOV 2011

Duration of Treatment:

52 weeks

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

Not applicable

Criteria for Evaluation

Efficacy:

The following nutritional evaluation items were to be assessed: body mass index (BMI), serum total protein, albumin, pre-albumin, total cholesterol, transferrin, retinol-binding protein, and Vitamin E using the FA subject sample.

Safety:

The safety evaluation was the primary analysis and was based on vital signs measurement, clinical laboratory evaluation, and AE monitoring.

Statistical Methods:

The FA subject sample was used for the analyses of the efficacy data. For the efficacy parameter (nutritional evaluation items) of the FA subject sample, summary statistics and 95% confidence interval (CI) was calculated using the observed values at each assessment time. Analyses using the available data at each visit were performed.

The Safety subject sample was used for the analysis of the safety and tolerability data. Adverse events were reported on a by-subject basis. This implied that even if a subject reported the same event repeatedly (that is, the same Preferred Term [PT]), the event was counted only once and assigned the worst severity and strongest relationship to the study medication. Cases of treatment-emergent adverse events (TEAEs) were presented by treatment group using a default frequency table.

Summary of qualitative laboratory test results were presented, combining all study centers, using default summary statistics, where percentage was calculated relative to the number of subjects in the Safety sample with applicable data available.

Laboratory measurement results for each laboratory variable, including change from Baseline (the level at the start of the study medication administration in the S245.3.123 study) 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 change from Baseline were summarized. Markedly abnormal vital signs were identified in accordance with pre-defined criteria.

All tests were done at the 5% level and 2-sided. No adjustments were done. No per protocol sample was defined.

Summary - Conclusions

Efficacy Results:

- In this study, SA-001 Capsule was administered at a basic dose of 3.0 g/day SA-001 (12 capsules/day) in the subjects analyzed. The majority of subjects remained on this dose and no major dose changes have been observed during the one-year treatment period which suggests that the prescribed dose of 3.0 g/day SA-001 covering main meals is a sufficient maintenance dose, since this dose has been administered on 71.5% of all treatment days.
- The final data set over one-year treatment with SA-001 showed for the mean of albumin an

increase from pathologically decreased to within the normal range. The mean values of total protein, total cholesterol, transferrin and retinol-binding protein were at the lower limit of the normal value at the beginning of the treatment period and showed a continued increase in maintaining the nutritional status. The mean values of pre-albumin increased over time but remained in the mean below the normal range. Whereas mean values of cholesterol, transferin and retinol-binding protein increased up to 24 weeks of treatment and were maintained during the remaining treatment period. The mean values for vitamin E did not show any significant changes over time.

- The mean values for BMI were abnormally low at baseline and increased continuously reaching the normal range during treatment with SA-001.

Safety Results:

- In this study, 80 subjects with PEI after pancreatic surgery due to pancreatic cancer or chronic pancreatitis were included. These subjects represent a population with a high mortality and morbidity which is associated with a relatively high incidence of AEs. The AEs observed in this study are the ones generally accompanying these underlying diseases.
- A total of 34 (42.5%) subjects reported 57 TESAEs. Nine subjects died. In total, 14 subjects prematurely withdrew from the study due to TEAEs. All these events were considered unrelated to the study medication administration by the Investigators, except for four TESAEs (hyperglycemia, pyrexia, gastric cancer, and aggravation of diabetes mellitus) and one TEAE which led to withdrawal (aggravation of hepatic function disorder), which were all considered unlikely related to the study medication. Most of the events were moderate to severe.
- Seventy-three (91.3%) subjects reported at least one TEAE and in total 508 TEAEs were recorded during the study.
- The most common reported SOCs were ‘Gastrointestinal disorders’, ‘Infections and infestations’, and ‘Metabolism and nutrition disorders’, mainly related to the underlying disease namely pancreatic cancer or chronic pancreatitis as primary disease or PEI as secondary disease.
- Thirty-eight (47.5%) subjects reported at least one event considered related to the study medication administration by the Investigator, mainly in the SOC ‘Gastrointestinal disorders’ and mostly of mild severity.
- The TEAEs considered to be severe were recurrent pancreatic carcinoma (n=6), metastases to liver (n=4), metastases to lymph nodes (n=3; one of duodenal cancer aggravated and one of aggravated pancreatic cancer), hypoglycemia (n=2), metastases to central nervous system, hepatic cancer metastatic, metastatic neoplasm, gastric cancer, malignant ascites, malignant lung neoplasm, cerebral hemorrhage, gastroenteritis *E. coli*, diabetes mellitus inadequate control, cholangitis, and epilepsy. All the events were considered unrelated to the study medication by the Investigator, except for gastric cancer, which was considered to be unlikely related to the study medication.
- More than 50% of the subjects reported a markedly increase in body weight.
- Since the morbidity of the study population is explaining the nature and incidence of the

AEs, SA-001 is considered to be safe and well tolerated.

Conclusion:

- The initial recommended dose of 3.0 g/day SA-001 covering main meals is considered to be the adequate maintenance dose.
- Nutritional parameters allover showed a continued increase, which is maintained during a one-year treatment period with SA-001 demonstrating an improvement and/or maintenance of the general nutritional status of chronic pancreatitis and pancreatectomy patients in this open-label long-term study.
- Since the morbidity of the study population is explaining the nature and incidence of the AEs, SA-001 is considered to be safe and well tolerated for long-term treatment