SYNOPSIS

Name of Sponsor: Abbott Seiyaku K.K.

Name of Finished Product: Undecided

Name of Active Ingredient: SA-001

Study Title: A Phase III Long-term Administration Study of SA-001 in the Treatment of Cystic Fibrosis

Final Report

Investigator(s): Removed for privacy reasons

Study Center(s): Removed for privacy reasons

Publication (Reference): Not applicable

Study Period: 14 NOV 2000 (first subject first visit) to 13 SEP 2010 (last subject last visit)

Phase of Development: III

Objectives:
To gather safety information on pancreatic enzyme supplementation with SA-001 administered, on a long-term basis, to patients with pancreatic exocrine insufficiency caused by cystic fibrosis.

Methodology:
From the day of subject’s documentation of informed consent to the day of manufacturing (import) approval of SA-001, subjects were to be given orally a 0.5-g sachet of SA-001 at doses up to 6.0 g/day (corresponding to 240,000 FIP units in labeled lipase activity in foreign countries) immediately after meals and snacks, in several divided doses depending on their eating habit. Subjects were to be monitored for subjective complaints, objective symptoms, adverse events, vital signs, height and weight, and laboratory assessments during the course of the study.
Number of Subjects (Planned, Consented, Randomized and Analyzed):
Number of subjects planned: 3 subjects
Number of subjects administered: 3 subjects
Number of subjects analyzed: 3 subjects

Supplementary explanation:
The clinical study (S.245.2.002) with SA-001 in patients with pancreatic exocrine insufficiency (PEI) caused by cystic fibrosis (CF) was carried out and five subjects were treated with SA-001. Among these subjects, two subjects died. For the other living three subjects, it was considered by their physicians that there was no alternative treatment other than treatment with SA-001. Therefore, three subjects were determined for sample size.

**Diagnosis and Main Criteria for Inclusion:**
Study subjects: patients PEI caused by CF

Inclusion Criteria:
- Subjects who are effectively treated with SA-001 in the previous clinical study in cystic fibrosis, and can not sufficiently be treated with any alternative treatment other than SA-001
- Subjects, or their proxy consenters (persons who have parental rights in general), who have documentation of informed consent prior to the initiation of treatment (since the study subjects are minors capable of giving their own consent)
- Subjects of either sex, regardless of age
- Either inpatients or outpatients

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

Test product: One gram of the preparation contains 600 mg of highly concentrated pancreatin (lipase activity per gram: 40,000 FIP-U/g in labeled activity in foreign countries).
In the study, a 0.5-g sachet is used; one sachet contains 0.3 g of highly concentrated pancreatin (lipase activity per sachet: 20,000 FIP-U in labeled activity in foreign countries).

Dose: Subjects are to be given orally a 0.5-g sachet of SA-001 at doses up to 6.0 g/day depending on their eating habit.

Mode of administration: Subjects are to be given orally the study medication immediately after meals and snacks. Subjects are to be advised (1) to swallow pellets without chewing and (2) to remove the residual pellets between teeth or in backside of the denture by gargling or tooth-brushing.

Lot number: S000704, K020401, K040204A, K051101A, S080616A

**Duration of Treatment:**
From the day of subject’s documentation of informed consent to the day of manufacturing (import) approval of SA-001

**Reference Therapy, Dose and Mode of Administration, Batch Number:**
Not applicable
Criteria for Evaluation

Efficacy:
Not Applicable
(This study was carried out to gather safety information of SA-001.)

Safety:
Presence or absence of adverse events.

Statistical Methods:
For each individual subject, results of assessments/testing were summarized, and safety evaluation was made as assessed by the absence/presence of adverse events to be counted by the causal relationship with the study medication; the absence/presence of adverse events were evaluated as assessed by subjective complaints/objective symptoms, findings in vital signs, and laboratory findings (hematology, blood chemistry, and urinalysis).

Summary - Conclusions

Efficacy Results:
Not applicable

Safety Results:

- For adverse events, 327 events were reported from three subjects; for all of the reported adverse events, the causal relationship to the study medication could be ruled out (unrelated or unlikely). Most of the reported adverse events were symptoms associated with respiratory disorders caused by CF.

- For serious adverse events, 27 events were reported from three subjects; for all of the reported serious adverse events, the causal relationship to the study medication was ruled out (unrelated or unlikely). One subject (Subject No. 1-C-1) died; this subject was hospitalized due to “cough aggravated” occurring on day 770; then, the underlying disease, CF, was aggravated, and the subject discontinued the study due to “respiratory failure”; the subject concomitantly had “renal failure NOS” and “shock”, and died 18 days after the discontinuation from the study. The death was judged to be unrelated to the study medication. Most of the reported other serious adverse events were symptoms caused by CF, including 13 events of “acute exacerbation of chronic bronchitis NOS”, three events of “pneumonia NOS”, one event of “right ventricular failure”, one event of “anaemia NOS”, and one event of “bronchitis chronic NOS”. For Subject No. 1-C-1, the subject had been repeatedly hospitalized for treatment of “acute exacerbation of chronic bronchitis NOS” eight times since the start of the study. In addition, all of the events observed in this subject were severe. Therefore, it appeared that the subject’s pathologic condition progressed over time. For Subject No. 1-C-2, “acute exacerbation of chronic bronchitis NOS” was not observed for one year and six months after the start of the study, but was reported on day 561. Since then, the subject had repeatedly experienced this event five times for about six months. Like Subject No. 1-C-1, the subject’s pathologic condition seemed to be making progress. “Right ventricular failure” and “anaemia NOS” reported from Subject No. 1-C-2 were judged to be due to CF condition; it appeared that the progress of “right ventricular failure” resulted from pulmonary hypertension, which was gradually making progress due to pulmonary fibrosis caused by CF and that the onset of “anaemia NOS” might be partly
because of malnutrition associated with the progress of CF condition and partly because of blood sampling for laboratory testing. Three events of “pneumonia NOS” were reported from Subject No. 2-CF-01. This subject more commonly had mild adverse events associated with CF condition, such as “cough” and “sputum”, than the other two subjects. However, the serious adverse events reported from this subject were only three events of “pneumonia NOS”, one event of “influenza”, and one event of “bronchitis chronic NOS”. In addition, the cause of some of the mild adverse events reported from this subject was explained as follows: since he felt well, he might overstrain himself; this might cause such mild symptoms. The pathologic condition in this subject was believed to be relatively more stable than in the other two subjects.

- As other serious adverse events, “renal impairment NOS” was reported from Subject No. 1-C-1 and “influenza”, “herpes viral infection NOS” were reported from Subject No. 1-C-2, and “influenza” was reported from Subject No. 2-CF-01. The reported “influenza” and “herpes viral infection NOS” in Subject No. 1-C-2 and “influenza” in Subject No. 2-CF-01 were considered to be due to viral infection; a number of common cold symptoms were also reported although they were not serious. These findings suggested that the progress of CF condition made the subject susceptible to infections. For “renal impairment NOS”, it was likely that antibiotic treatment for “acute exacerbation of chronic bronchitis NOS” might lead to this event. After the occurrence of “renal impairment NOS”, the subject discontinued intravenous administration of tobramycin and piperacillin sodium while continuing SA-001 treatment. Then, the renal function was normalized. Based on these outcomes, the physician judged this event as “unlikely” to be related to the study medication. Any of the reported other serious adverse events than the death due to the progress of CF condition disappeared or lightened over time, with the exceptions of unchanged symptoms of one event of “acute exacerbation of chronic bronchitis NOS”, one event of “right ventricular failure”, and one event of “anaemia NOS”, which were reported from Subject No. 1-C-2, and one event of “bronchitis chronic NOS” which was reported from Subject No. 2-CF-01. Subject No. 1-C-2 discontinued the study by day 1219, and left for the U.S.A. to undergo lung transplantation. Subject No. 2-CF-01 discontinued the study on day 3591 because of a planned lung transplantation. This subject got lost to follow-up.

- As other significant adverse events, in addition to “acute exacerbation of chronic bronchitis NOS”, “pneumonia NOS”, and “bronchitis chronic NOS” as described above, symptoms associated with respiratory disorders such as “cough” and “sputum” were commonly reported although they were not serious. The reason for commonly reported respiratory symptoms was explained as follows: CF patients have an inherent risk of developing abnormally viscous external secretory fluids, leading to bronchial obstruction, which can cause various respiratory symptoms.

- All these subjects received 6.0 g/day of SA-001 until the day of the discontinuation of the study.

**Conclusion:**

SA-001 was confirmed to be clinically safe in this study for the long-term treatment of three subjects with PEI caused by CF.