2 SYNOPSIS

Sponsor: **Shionogi, Inc.**	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Not Applicable	**Volume:**	
Name of Active Ingredient: S-888711	**Page:**	

Study Title:
An open-label safety study of S-888711 in adult subjects with relapsed persistent or chronic immune thrombocytopenia with or without prior splenectomy

Investigators and Study Centers: Multicenter (see Appendix 16.1.4)

Publication (reference): Not applicable

Studied Period:

[redacted] April 2010 (first subject enrolled) to
June 2011 (last subject completed – Study Terminated by the Sponsor)

Phase of Development: 2

Objectives:

Primary Objective:

- To assess the long-term safety of S-888711

Secondary Objectives:

- To assess dose requirements for long-term platelet response
- To assess durability of platelet response
- To evaluate bleeding events by World Health Organization (WHO) bleeding criteria

Exploratory Objective:

- To evaluate the bone marrow histology in subjects electing to undergo serial bone marrow biopsies during the administration of S-888711

Methodology: This was a multicenter, open-label, long-term safety study of S-888711 in the treatment of subjects with relapsed persistent or chronic immune thrombocytopenia (ITP) with or without prior splenectomy. Eligible subjects previously participated in Study 0913M0621, a double-blind, placebo controlled, parallel group study, that evaluated the efficacy and safety of S-888711 during which they either completed treatment or discontinued treatment due to a platelet count > 400,000/μL.

Assessments performed during the Final/Early Termination Visit of Study 0913M0621 served as the initial screening visit for this open-label, long-term safety study. Subjects signed another informed consent indicating their agreement to participate in this long-term safety study and inclusion/exclusion criteria were reviewed to determine the subject's eligibility to participate in this study.

Platelet counts were determined when a subject was ready to begin dosing. If a subject's platelet count was < 50,000/μL, the subject was eligible to enter the Dose Adjustment Period

directly from the final visit of Study 0913M0621. For these subjects, exams performed at the Final/Early Termination Phase 2 Visit served as baseline for this long-term safety study. Subjects could immediately start dosing with S-888711 0.5 mg (Day 1).

To assess the bone marrow histology under treatment with S-888711, subjects were given the opportunity to participate in serial bone marrow biopsies annually (based on the subject's start date in the Open-Label Extension Study, at the investigator's discretion). These exams were optional. In addition, bone marrow biopsies to assess potential bone marrow fibrosis were performed as indicated for subjects with suggestive abnormal peripheral smears (eg, anemia, neutropenia, increased immature cells). For those subjects with evidence of fibrosis on bone marrow examination, treatment was stopped and a follow-up bone marrow biopsy was obtained 2 months after treatment cessation; thereafter, further diagnostics and treatment were at the discretion of the investigator.

Treatment Qualifying Period: If the platelet count was ≥ 50,000/μL, the subject was to have a platelet count performed weekly until the subject's count was < 50,000/μL, at which time the subject was eligible to enter the Dose Adjustment Period and start dosing with S-888711 0.5 mg (Day 1). If the Treatment Qualifying Period extended beyond 4 weeks, a full screening evaluation was performed, and repeated every 4 weeks thereafter until the subject qualified for dosing. These exams became the treatment baseline for these subjects. The sponsor's medical monitor was contacted for any subject whose Treatment Qualifying Period exceeded 8 weeks.

Dose Adjustment Period: On Day 1, all subjects started with the 0.5 mg dose administered orally once daily. Evaluations were performed weekly. At the Week 2 (or Week 3 at the Principal Investigator's [PI] discretion) visit:

- If a subject's platelet count remained < 50,000/μL, the dose could have been increased by 0.25 mg, unless in the opinion of the investigator, this was an acute or transient result of infection or other intercurrent illness. Subsequent dose increases in 0.25 mg increments were allowed up to 1.0 mg and then by 0.50 mg increments up to a maximum dose of 2.0 mg. If the platelet count remained < 50,000/μL, despite treatment with the 2.0 mg dose, continued treatment was contingent on agreement between the sponsor's medical monitor and the investigator.
- If a subject's platelet count was between 50,000/μL to 400,000/μL (inclusive), no adjustment was required, and the subject entered the Maintenance Period.
- If, at any time during the Dose Adjustment Period, a subject's platelet count rose to > 400,000/μL, the S-888711 dose could be decreased by 0.25 mg, unless in the opinion of the investigator, this was an acute or transient result of infection or other intercurrent illness. If the platelet count remained > 400,000/μL after 1 week on a reduced dose, the S-888711 dose could be decreased by an additional 0.25 mg per week or if the subject was already receiving the 0.25 mg dose, treatment was discontinued. Reintroduction of study drug was at the discretion of the sponsor's medical monitor and the investigator.

Any time a subject required dose adjustment (increase or decrease), the subject reverted back to Week 1 of the Dose Adjustment Period. Following office visits, the investigative site called the subject to inform him/her of platelet test results, and if necessary, gave instructions for dose adjustments and made arrangements for additional medication to be provided if an increase was needed. These contacts were documented in subject's study documents.

Maintenance Period: Once a subject's platelet count was between 50,000/µL to 400,000/µL (inclusive) at the Week 3 visit, the subject continued to be evaluated weekly for an additional 3 weeks. If the S-888711 dose did not require adjustment within this evaluation period, the visit intervals could be widened to every 4 weeks (monthly). After 3 monthly evaluations with a stable S-888711 dose requirement, visit intervals could be widened to every 3 months thereafter.

If, at any time during the Maintenance Period, a subject's platelet count fell outside the range of 50,000/µL to 400,000/µL, a dose adjustment could be made after discussion and approval by the sponsor's medical monitors, and the subject reverted back to Week 1 of the Dose Adjustment Period.

Follow-up Period: Following discontinuation of treatment in this long-term safety study, subjects were followed weekly for 6 weeks for the determination of platelet counts, prior/concomitant medication recording, and adverse events (AEs).

Subjects who had an abnormal peripheral blood smear with evidence of fibrosis on bone marrow examination were discontinued from treatment and a repeat bone marrow biopsy was obtained 2 months after treatment cessation; thereafter, further diagnostics and treatment were at the discretion of the investigator. These subjects were followed for AEs during this 2-month period.

Number of Patients (Planned and Analyzed):
Sample size was determined by the number of subjects who chose to enter this open-label study; 19 subjects were analyzed for safety; 19 subjects were analyzed for efficacy.

Diagnosis and Main Criteria for Inclusion:
Male and female subjects ≥ 18 years of age with relapsed persistent or chronic ITP with or without prior splenectomy who previously participated in Phase 2 ITP Study 0913M0621 and who either completed treatment or discontinued treatment due to a platelet count > 400,000/µL were eligible for participation. Subjects must have continued to meet all inclusion criteria of the previous study including platelet counts < 50,000/µL to be eligible for study participation.

Test Product, Dose and Mode of Administration, Lot Number:
S-888711 was supplied as a 0.25 mg light red film-coated tablet for oral administration.
Initial dose: 0.5 mg; dose range: 0.25 mg up to 2.0 mg.

Lot number: [redacted], [redacted], and [redacted].

Duration of Treatment: S-888711 was administered once daily, without regard to meals. Subjects were instructed to take the study drug at approximately the same time each day. The study was planned to continue for a period of up to three (3) years or until S-888711 was commercially available, or Shionogi, Inc. discontinued research on S-888711 for this indication.

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

Criteria for Evaluation:

Efficacy:
Efficacy endpoints included:

- Duration of response (DR), defined as the proportion of the cumulative time spent with a platelet count ≥ 50,000/µL

- The incidence and worst severity of bleeding associated with ITP
- The proportion of subjects who achieved a platelet count of < 50,000/μL, 50,000/μL ≤ platelet count ≤ 400,000/μL, > 400,000/μL
- The proportion of subjects who achieved a platelet count of < 50,000/μL, 50,000/μL ≤ platelet count ≤ 400,000/μL, > 400,000/μL, not including platelet counts measured while the subject was taking rescue medication and for the 4 weeks after rescue medication
- Final platelet counts and the change from baseline in platelet counts.
- Platelet counts plotted with rescue medication information

Safety:

Safety was assessed by monitoring AEs, clinical laboratory evaluations (including hematology, blood biochemistry, urinalysis, blood smears), vital signs, physical examinations, and electrocardiograms. Treatment-emergent AEs (TEAEs) and serious adverse events (SAEs) were collected and tabulated.

To assess the bone marrow histology under treatment with S-888711, subjects were given the opportunity to participate in serial bone marrow biopsies annually (based on the subject's start date in the Open-Label Extension Study, at the investigator's discretion). These examinations were optional. In addition, bone marrow biopsies to assess potential bone marrow fibrosis were required as indicated for subjects with suggestive abnormal peripheral smears (eg, anemia, neutropenia, increased immature cells). For those subjects with evidence of fibrosis on bone marrow examination, treatment was stopped and a follow-up bone marrow biopsy was obtained 2 months after treatment cessation; thereafter, further diagnostics and treatment were at the discretion of the investigator.

Statistical Methods:

Statistical analysis was performed using SAS® Version 9.2. Unless otherwise noted, continuous endpoints were summarized using the number of non-missing observations (n), mean, standard deviation (SD), median, and range. Categorical endpoints were summarized using frequencies and percentages of subjects in each category.

Periodic safety summaries were to be prepared and provided to the Data and Safety monitoring Board (DSMB), but the study was cancelled before the DSMB was finalized.

Efficacy:

Efficacy endpoints were summarized descriptively.

Safety:

Number and percentage of subjects who experienced TEAEs were tabulated and summarized by severity and relationship to study drug. Descriptive statistics are provided for laboratory data and shifts from baseline were summarized.

Summary of Results

Efficacy:

- When treatment response was determined including platelet counts measured when the subject was taking rescue medications, 13 of the 19 subjects (68.4%) achieved a platelet count of 50,000/μL to 400,000/μL, and 6 subjects (31.6%) had a platelet count < 50,000/μL. Without the use of rescue medications, 11 subjects (57.9%) achieved a platelet count of 50,000/μL to 400,000/μL and 8 subjects (42.1%) had a

platelet count < 50,000/μL. No subjects achieved a platelet count > 400,000/μL.

- For 10 of the 19 subjects (52.6%) in the study, platelet count transiently increased with doses of 1.0 to 2.0 mg S-888711. Three of the 7 subjects (42.8%) who received 1 or 1.5 mg S-888711 achieved a platelet count > 50,000/μL; and 7 of the 11 subjects (63.6%) who received 2 mg S-888711 achieved a platelet count > 50,000/μL.
- Median DR (the proportion of the cumulative time a platelet count was ≥ 50,000/μL), was 0.20 (range: 0.0-0.80). Median platelet count was the same (23,000/μL) at baseline and at the final time point; however, platelet count was more variable and increased at the final timepoint (range: 4000/μL to 124,000/μL) than at baseline (range: 9000/μL to 40,000/μL). Median change in platelet count from baseline to the final time point was 3000/μL.
- Most subjects (84.2%) had a bleeding incidence associated with ITP; the severity of any bleeding incidence did not exceed Grade 2.

Safety:

- Nineteen subjects (100.0%) reported 167 TEAEs during the study, including 3 subjects (15.8%) who reported 9 treatment-related TEAEs. No subjects died during the study period. Three SAEs (thrombocytopenia, overdose, and suicidal ideation) were reported in 1 subject ([redacted]) and considered not related to treatment.
- Four TEAEs led to study drug withdrawal for 2 subjects (10.5%); these were hematoma that was considered not related to treatment, and pruritus, urticaria, and erythema, that were considered possibly related to treatment. These TEAEs resolved within 2 weeks after onset.
- Most TEAEs reported during this study were mild (9 subjects, 47.4%) or moderate (8 subjects, 42.1%) in severity; 2 subjects (10.5%) experienced a total of 3 TEAEs considered severe. Severe TEAEs were diarrhea, migraine, and platelet count decreased, considered not related to study treatment and were non-serious. These severe events resolved (platelet count decreased resolved with sequelae).
- Frequently reported TEAEs (those reported by 2 or more subjects) were nasopharyngitis, fatigue, cough, arthralgia, contusion, upper respiratory tract infection, ecchymosis, nausea, oropharyngeal pain, vomiting, pain in extremity, back pain, blood potassium decreased, CRP increased, insomnia, mouth hemorrhage, myositis, nasal congestion, edema peripheral, and urinary tract infection.
- Nine treatment-related TEAEs were reported in 3 subjects (15.8%), these were moderate bone marrow reticulin fibrosis, atrial fibrillation, fatigue (2 events), urticaria, mild nausea, insomnia, erythema, and pruritus. Relatedness to S-888711 was considered possibly related for all the treatment-related TEAEs with the exception of bone marrow reticulin fibrosis which was assessed as probably related. These treatment-related TEAEs were mild or moderate.
- No clinically significant mean changes in any laboratory parameter, vital signs, or physical examination, or clinically relevant ECG finding, were observed.

CONCLUSIONS

Efficacy Conclusions:

The number of adult subjects with relapsed persistent or chronic ITP, with or without prior splenectomy, who achieved a sufficient platelet count response, increased when the dose of S-888711 was 1 mg or greater per day.

Safety Conclusions:

Administration of oral once-daily 0.5 to 2.0 mg S-888711 to adult subjects with relapsed persistent or chronic ITP with or without prior splenectomy was well-tolerated.

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