

## 2 SYNOPSIS

**Sponsor:** Shionogi Inc.                      **Individual Study Table**                      **(For National Authority Use only)**

**Name of Finished Product:** S-888711                      **Referring to Part of the Dossier**

**Name of Active Ingredient:** S-888711                      **Volume:**

**Name of Active Ingredient:** S-888711                      **Page:**

**Study Title:**

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of S-888711 tablets administered once-daily for 42 days to 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):** see [Appendix 16.1.11](#)

**Studied Period:**

March 2010 (first subject enrolled) to  
November 2010 (last subject completed)

**Phase of Development:** 2

**Objectives:**

**Primary Objective:**

- To assess the efficacy of 3 dose levels of S-888711 (0.5 mg, 0.75 mg, and 1.0 mg) and placebo on platelet count.

**Secondary Objectives:**

To assess the:

- Safety of S-888711;
- Pharmacokinetic (PK) profile of S-888711 using sparse PK sampling;
- PK profile of S-888711 using serial PK sampling in a selected subset of subjects;
- Pharmacodynamic (PD) effect of S-888711 on platelet count and markers of platelet function, such as endogenous thrombopoietin (TPO);
- PK/PD relationship of S-888711 with respect to platelet count; and
- Impact of S-888711 on the incidence and severity of bleeding.

**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 Phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study to evaluate the efficacy, safety, PK, and PD of S-888711 in the treatment of subjects with relapsed persistent or chronic immune thrombocytopenia (ITP) with or without prior splenectomy.

Eligible subjects who signed informed consent returned to the study site for randomization (Visit 1, Day 1) into the Double-Blind Treatment Period. During the Double-Blind Treatment Period, subjects were evaluated weekly (every 7 days  $\pm$  1 day; Visit 2 through the Final Visit) for efficacy, safety, PK, and PD while receiving S-888711 or placebo.

At the Final Visit, subjects who completed the Double-Blind Treatment Period may have been eligible to rollover into the Open-Label Extension Study ([Study Number: 0914M0622](#)). In addition, any subject whose platelet count increased to  $> 400,000/\mu\text{L}$  in the Double-Blind Treatment Period was withdrawn and may have been eligible to enter into the Open-Label Extension Study. Subjects who did not rollover into the Open-Label Extension Study had 6 weekly Follow-up Visits to assess safety.

**Number of Subjects (Planned and Analyzed):**

Approximately 60 subjects were planned; 20 subjects were enrolled and were analyzed for safety and efficacy. This study was terminated early before the planned sample size was enrolled because results indicated that a higher dose was necessary to elicit an efficacy effect.

**Diagnosis and Main Criteria for Inclusion:**

Medically stable male and female subjects  $\geq 18$  years of age with relapsed persistent or chronic ITP with or without prior splenectomy were eligible for participation.

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

S-888711 0.25 mg light red film-coated tablet for oral administration. Three groups received different doses of S-888711: 0.5 mg (2 S-888711 tablets + 2 matching placebo tablets); 0.75 mg (3 S-888711 tablets + 1 matching placebo tablet); and 1.0 mg (4 S-888711 tablets).

Lot number: [REDACTED] (active drug; [Appendix 16.1.6](#)).

**Duration of Treatment:** S-888711 or matching placebo was administered once daily, without regard to meals, for 42 days. Subjects were instructed to take the study drug at approximately the same time each day.

**Reference Therapy, Dose and Mode of Administration, Lot Number:**

Placebo tablet matching the S-888711 0.25 mg tablet for oral administration. The placebo group was dosed with 4 placebo tablets. Lot numbers: [REDACTED] and [REDACTED].

**Criteria for Evaluation:**

**Efficacy:**

The primary assessments of efficacy were platelet counts (collected as part of the complete blood count and bleeding evaluation). For this study, subjects were classified as responders if they:

- Achieved a platelet count of  $\geq 50,000/\mu\text{L}$  after 6 weeks of dosing; or
- Were prematurely withdrawn due to a platelet count  $> 400,000/\mu\text{L}$  prior to Day 42.

Subjects who did not meet the above condition, had received rescue medications during the Double-Blind Treatment Period, or who were withdrawn for any reasons other than a platelet count  $> 400,000/\mu\text{L}$  were counted as non-responders.

The primary efficacy endpoint was the proportion of responder subjects in each treatment group.

Secondary efficacy endpoints included:

- Change from baseline in platelet count after 6 weeks of dosing;

- Duration of response in each treatment group from Visit 1 (Day 1) to the Final Visit (Day 43), defined as the proportion of the cumulative time spent platelet count was  $\geq 50,000/\mu\text{L}$  during the treatment period;
- Proportion of subjects in each treatment group who achieved a platelet count of  $\geq 30,000/\mu\text{L}$  and double the baseline platelet count after 6 weeks of dosing;
- Proportion of subjects in each treatment group who achieved a platelet count of  $\geq 50,000/\mu\text{L}$  and double the baseline platelet count after 6 weeks of dosing;
- Incidence and severity of bleeding associated with ITP during the treatment period; and
- Proportion of subjects in each treatment group who received rescue medication at any time during the treatment period.

#### **Pharmacokinetic Assessments:**

Blood samples were collected for PK analysis of S-888711 and its metabolites (S-888711 deshexyl and S-888711 5-keto). All subjects participated in sparse PK sampling with 1 sample collected after dosing on Days 8, 22, and 36. One subject participated in optional serial PK sampling with samples collected prior to dosing and at 2, 4, 6, and 8 hours after dosing on Days 1 and 8.

#### **Safety:**

Safety was assessed by monitoring clinical laboratory evaluations (including hematology, blood biochemistry, thyroid function, and urinalysis), vital signs, 12-lead electrocardiograms (ECG), physical examinations, and World Health Organization (WHO) bleeding assessments, and adverse events (AEs). Treatment-emergent AEs and serious AEs (SAEs) were collected and tabulated. Blood samples for peripheral blood smear were collected at Screening. For subjects not going into the Open-Label Extension Study, a peripheral blood smear was performed at the Final Visit/Early Termination.

#### **Exploratory:**

Subjects were given the opportunity to participate in optional serial bone marrow biopsies at Screening and the Final Visit/Early Termination to assess the bone marrow histology under treatment with S-888711. No serial bone marrow biopsies were performed.

#### **Statistical Methods:**

All data collected were summarized using appropriate descriptive statistics. Statistical tests were performed at the 0.05 significance level using 2-sided tests, except where otherwise noted.

#### **Efficacy:**

The primary efficacy analysis was the Cochran-Armitage trend test at the 0.025 level of significance (1-sided) for detecting the dose-response relationship of S-888711 to support proof of concept. The proportion of responders in each S-888711 treatment group was compared to placebo to explore treatment effect.

#### **Pharmacokinetic:**

Descriptive statistics (e.g., n, mean, SD, coefficient of variation [CV%], median, minimum, maximum, geometric mean, and 95% confidence intervals for geometric mean) of plasma concentrations for S-888711, S-888711 deshexyl, and S-888711 5-keto, are presented for full PK profiling days in tabular form by treatment group, study day, and nominal time. Linear

plots of median plasma concentrations by treatment and PK sampling days for S-888711 plasma concentrations are presented. Other PK analyses are described in separate documents provided by Shionogi.

**Safety:**

Number and percentage of subjects who experienced treatment-emergent AEs were tabulated and summarized by severity and relationship to study drug. Descriptive statistics are provided for laboratory data and for tests with available post-baseline data, shifts from baseline were summarized.

**Summary of Results**

**Efficacy:**

- With the exception of 1 subject (██████) in the 0.5 mg treatment group, no responders (platelet count  $\geq 50,000/\mu\text{L}$  after 6 weeks of dosing at the Final Visit without the use of rescue medication) were found in any of the 3 remaining treatment groups; no dose-response relationship was apparent in the proportion of responders in this study (by Cochran-Armitage Trend Test,  $p = 0.431$ ).
- Two subjects in the 0.5 mg treatment group and 1 subject each in the 0.75 and 1.0 mg treatment group met the definition of a responder at a study visit (i.e., platelet count  $\geq 50,000/\mu\text{L}$  prior to any rescue or restricted medication). None of the subjects in the placebo group met the definition of a responder at an individual study visit.
- Platelet count increased from baseline in the 0.5 and 0.75 mg treatment groups and decreased from baseline in the placebo and 1.0 mg treatment groups; platelet count did not increase from baseline in a dose-dependent manner.
- Median DR (the proportion of the cumulative time a platelet count was  $\geq 50,000/\mu\text{L}$  during the Double-blind Treatment Period) was 39.9%, 42.6%, and 10.3% in the 0.5, 0.75, and 1.0 mg treatment groups whereas the maximum platelet count was  $25,000/\mu\text{L}$  in the placebo group.
- After 6 weeks of dosing, 3 subjects (60.0%) in the 0.5 mg treatment group and 1 subject (20.0%) in the 0.75 mg treatment group achieved a platelet count  $\geq 30,000/\mu\text{L}$  that was doubled from baseline, and 2 subjects (40.0%) in the 0.5 mg treatment group achieved a platelet count of  $\geq 50,000/\mu\text{L}$  that was doubled from baseline (1 subject [██████] was classified as a responder; the other subject [██████] received rescue medication and so was not classified as a responder).
- With the exception of 2 subjects in the 0.75 mg treatment group, all subjects had bleeding. Bleeding associated with ITP did not exceed Grade 2 during the treatment period. No dose-response relationship was found in the worst severity of bleeding.
- No dose-dependent decrease was found in the proportion of subjects who received rescue medication between placebo and 0.5 to 1.0 mg/day of S-888711.

**Pharmacokinetics Summary:**

- S-888711 plasma concentration appeared steady across Days 8, 22, and 36 in each S-888711 dose group.

## Safety:

- A total of 63 treatment-emergent AEs occurred in 18 of 20 subjects (90.0%) overall: 5 of 5 subjects (100.0%, 15 events) in the 0.5 mg treatment group, 5 of 5 subjects (100.0%, 12 events) in the 0.75 mg treatment group, 4 of 5 subjects (80.0%, 13 events) in the 1.0 mg treatment group, and 4 of 5 subjects (80.0%, 23 events) in the placebo group. The incidence of treatment-emergent AEs did not increase with the increase in dose of S-888711.
- Frequent treatment-emergent AEs (i.e., those reported by at least 2 of 20 subjects) which were only reported in S-888711 treatment groups were contusion, upper respiratory tract infection, hot flush, and platelet count decreased. Contusion was reported by 3 subjects in the 0.5 mg treatment group and the other AEs were reported in 0 or 1 subject in a treatment group.
- One SAE (moderate renal vein thrombosis), considered unrelated to study treatment, was reported by 1 subject in the 1.0 mg treatment group.
- No subject had action taken of study drug withdrawn due to an AE and no deaths occurred on study.
- Five treatment-emergent AEs were considered possibly related to the study treatment: 1 of 5 subjects (20.0%, 1 event) in the 0.5 mg treatment group, 2 of 5 subjects (40.0%, 3 events) in the 1.0 mg treatment group, and 1 of 5 subjects (20.0%, 1 event) in the placebo group. Treatment-related AEs reported in this study were upper abdominal pain, musculoskeletal stiffness, pain in the extremity (each in the 1.0 mg treatment group), nausea (0.5 mg treatment group), and insomnia (placebo). Other treatment-emergent AEs were considered unrelated to the study treatment.
- No clinically significant changes in any laboratory parameter, vital signs, physical examination, or ECG were found.

## CONCLUSIONS

### Efficacy Conclusions:

- With the exception of 1 subject (██████) in the 0.5 mg treatment group, no responders (platelet count  $\geq 50,000/\mu\text{L}$  after 6 weeks of dosing at the Final Visit without the use of rescue medication) were found in any of the 3 remaining treatment groups.
- No dose-response relationship was demonstrated when 0.5, 0.75, or 1.0 mg of S-888711 was administered orally once-daily for 42 days to adult subjects with relapsed persistent or chronic ITP with or without prior splenectomy.

### Pharmacokinetics Conclusions:

- S-888711 plasma concentration appeared steady across Days 8, 22, and 36 in each S-888711 dose group.

### Safety Conclusions:

- Administration of oral once-daily 0.5, 0.75, or 1.0 mg S-888711 for 42 days to adult subjects with relapsed persistent or chronic ITP with or without prior splenectomy was well-tolerated.

- Treatment-related AEs reported in this study were upper abdominal pain, musculoskeletal stiffness, pain in the extremity (each in the 1.0 mg treatment group), nausea (0.5 mg treatment group), and insomnia (placebo).

This study was terminated early before the planned sample size was enrolled because results indicated that a higher dose was necessary to elicit an efficacy effect.

**Final Report Date:** 30 June 2011

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