2. SYNOPSIS

English Translation (The original report was written in Japanese)

Name of Sponsor: Shionogi & Co., Ltd. **Name of Finished Product:** To be determined **Name of Active Ingredient:** S-888711	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	(For National Authority Use Only)
Title of Study: A three-way crossover study to assess the relative bioavailability of 1-mg and 4-mg tablets of S-888711 and the effect of high-fat meals on the pharmacokinetics of the 4-mg tablet in healthy male subjects		
Investigators: [redacted]		
Study Centers: [redacted]		
Publication: None		
Study Period: Two months between February [redacted], 2013 (date of the first administration of the study drug to the first subject) and March [redacted], 2013 (date of the final observation for the last subject)		
Phase of Development: 1		

Study Objectives:

Primary Objectives:

- To compare the pharmacokinetics (PK) of S-888711 at a 4-mg single dose using a 4-mg tablet with those using a 1-mg tablet.
- To assess the effect of food on the PK of S-888711 at a 4-mg single dose using a 4-mg tablet.

Secondary Objective:

- To assess the safety and tolerability of S-888711 in single-dose administration.

Methodology:

This study was a single center, randomized, 3-way crossover study in 15 healthy adult male subjects.

The study consisted of the Screening Period (1 to 28 days), the Crossover Period (40 days [13 days × 3 periods + 1 day]), and the Final Assessment Period (1 day). Eligible subjects (ie, subjects who were considered eligible in the Screening Period) were enrolled in the study and were randomized to any of the 3 regimen sequences (5 subjects per sequence). Randomized subjects received the study drug at a single dose according to the assigned regimen sequence (1-mg tablet in the fasted state, 4-mg tablet in the fed state, and 4-mg tablet in the fasted state).

For subjects receiving the study drug in the fasted state, subjects received the study

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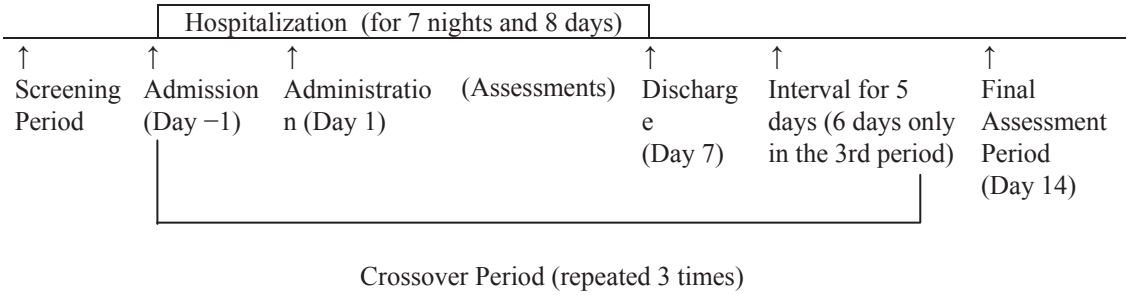
drug following at least 10 hours of fasting after completion of evening meal on the previous day of administration of the study drug. For subjects receiving the study drug in the fed state, subjects received the study drug after taking a high-fat breakfast.

Randomized subjects underwent assessments in the Crossover Period and the assessments were repeated 3 times. The washout interval was 12 days. The Final Assessment was performed on Day 14 in the third period. Pre-dosing assessments on Day 1 in the second and the third period included the meaning as the Final Assessments on Day 14 in the first and second period.



Number of Subjects:

Planned target sample size: 15 subjects

Enrolled subjects: 15 subjects

Administered subjects: 15 subjects

Analysis population is as follows:

- Pharmacokinetic analysis population: 15 subjects
- Safety analysis population: 15 subjects

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria:

Subjects who fulfilled all of the following criteria were included in the study:

1. Subjects who were able to understand the study and comply with all study procedures, and willing to provide written informed consent prior to screening.
2. Male subjects aged ≥ 20 and < 40 years at the time of signing the informed consent form.
3. Subjects who were considered to be healthy at the screening assessment.
4. Subjects whose body weight was ≥ 50 and ≤ 80 kg and body mass index (BMI) was

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≥ 18.5 and < 25.0 (kg/m^2).

5. Subjects with platelet count within the reference range and platelet count of 300,000/μL or less at screening.
6. Subjects who agreed to use appropriate methods of contraception (eg, the use of a condom with spermicide) between the admission day (Day −1) and 3 months after the last dose of study drug.

Exclusion Criteria:

Subjects who met any of the following criteria were excluded from the study:

1. Subjects who had a history of cardiac episode and abnormal finding on electrocardiogram (ECG) and who were considered to be ineligible by the investigator or subinvestigator.
2. Subjects who had chronic disease requiring medication and other treatments such as dietary restriction and physical therapy.
3. Subjects who had a history of nervous, gastrointestinal, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, hematic and other clinically important disorder and were considered ineligible by the investigator or subinvestigator.
4. Subjects whose family had a history of thrombosis, coagulation disorder, or thrombocytosis.
5. Subjects who had a history of an operation, such as excision of stomach, vagal nerve and gut except for appendectomy.
6. Subjects who had a hemorrhagic tendency.
7. Subjects who received any drugs (eg, prescription drugs, over-the-counter drugs, Chinese herbal medicines, supplements, vitamins) within 3 days prior to screening.
8. Subjects who smoked or used smoking cessation aid containing nicotine within 24 weeks prior to screening.
9. Subjects who received cytochrome-P450 inhibitors (eg, itraconazole) or inducers (eg, rifampicin) within 4 weeks prior to screening.
10. Subjects who received the following drugs which decrease platelet aggregation ability within 4 weeks prior to screening: nonsteroidal anti-inflammatory drugs (eg, aspirin), coronary vasodilators (eg, dipyridamole), Ca-antagonists (eg, nifedipine), β-blockers (eg, atenolol), diuretics (eg, furosemide), psychotropic drugs (eg, chlorpromazine), prostaglandins (eg, Prostandin), antibiotics (eg, penicillin), anticoagulants (eg, heparin), antiplatelet drugs (eg, ticlopidine).

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11. Subjects who received thrombocytopenia-inducing drugs (eg, quinidine, valproic acid) within 4 weeks prior to screening.
12. Subjects who received hematinic drugs (eg, epoetin alfa) within 4 weeks prior to screening.
13. Subjects who received drugs or supplements inducing platelet aggregation (eg, vitamin K) within 4 weeks prior to screening.
14. Subjects who donated 400 mL or more of blood within 12 weeks prior to screening or 200 mL or more of blood (including platelet and plasma component) within 4 weeks prior to screening.
15. Subjects who had a history of anaphylaxis or serious side effect induced by a drug.
16. Subjects who had a history of allergic symptoms including food allergy but excluding inactive pollen disease.
17. Subjects who had a history of addiction to alcohol or drug.
18. Subjects whose urine was positive in urine screening tests for drug abuse.
19. Subjects who had positive test results for serologic test for syphilis, Treponema pallidum, hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficient virus antibody/antigen.
20. Subjects who were not able to obey items listed in "6. Restrictions" in the study protocol.
21. Subjects who had been exposed to other investigational drugs within 16 weeks prior to the day of administration of the study drug in the first period.
22. Subjects who had received S-888711 or thrombopoietin (TPO) agonists previously.
23. Subjects who were considered inappropriate for the study by the investigator or subinvestigator.

Test Drug, Dose and Mode of Administration, Lot Number:

Test Drug (S-888711):

S-888711 1-mg tablet, S-888711 4-mg tablet

Dose:

- Single dose of S-888711 4 mg

Method of Administration:

Randomized subjects received a 4-mg tablet or 1-mg tablets of S-888711 with water of 200 mL at an oral single dose in the fasted state or in the fed state on Day 1 in each period.

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- Regimen A (1-mg tablet/fasted state): Four 1-mg tablets of S-888711 were orally administered at a single dose in the fasted state.
- Regimen B (4-mg tablet/fed state): One 4-mg tablet of S-888711 was orally administered at a single dose in the fed state.
- Regimen C (4-mg tablet/fasted state): One 4-mg tablet of S-888711 was orally administered at a single dose in the fasted state.

Lot Number (Manufacturing Number):

S-888711 1-mg tablet, [redacted]

S-888711 4-mg tablet, [redacted]

Control Drug, Dose and Mode of Administration, Lot Number:

No control drug was used in this study.

Duration of Administration: A single dose (1 day) in 3 periods of the Crossover Period.

Criteria for Evaluation:

Pharmacokinetic Variables:

Plasma S-888711 concentration and pharmacokinetic parameters, including maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the concentration-time curve from time zero to the time of the last quantifiable concentration after dosing ($AUC_{0\text{-last}}$), area under the concentration-time curve extrapolated from time zero to infinity ($AUC_{0\text{-inf}}$), terminal elimination rate constant (λ_z) , terminal elimination half-life ($t_{1/2,z}$), apparent total clearance (CL/F), and mean residence time (MRT).

Safety Assessment:

Physical examinations, vital signs, electrocardiograms, clinical laboratory tests, and adverse events (AEs).

Statistical Methods:

Pharmacokinetics

PK parameters of S-888711 were calculated based on the plasma S-888711 concentrations by using model independent approach. PK of each tablet in the fasted state was compared and an influence of food on PK parameters at a 4-mg single dose was evaluated by using the analysis of variance (ANOVA).

Safety

The number of subjects who experienced any AEs and the incidence were summarized

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by treatment group. The number of AEs was summarized. The same summaries were presented for adverse drug reactions.

Summary - Conclusions

Pharmacokinetic Results:

The table below shows PK parameters in each treatment group.

Treatment group	N	C_{max} [a] (ng/mL)	T_{max} [b] (hr)	$AUC_{0\text{-last}}$ [a] (ng·hr/mL)	$AUC_{0\text{-inf}}$ [a] (ng·hr/mL)	$t_{1/2,z}$ [a] (hr)	CL/F [a] (L/hr)	MRT [a] (hr)
1-mg tablet/fasted	15	179 (17.0)	4.0 (4.0-10)	5124 (17.0)	5220 (17.4)	26.1 (11.6)	0.766 (17.4)	33.5 (9.5)
4-mg tablet/fasted	15	165 (20.3)	4.0 (4.0-10)	4685 (20.9)	4776 (21.5)	27.0 (10.8)	0.837 (21.5)	33.5 (12.7)
4-mg tablet/fed	15	151 (18.7)	4.0 (3.0-5.0)	4256 (22.1)	4336 (22.6)	26.5 (11.2)	0.923 (22.6)	33.2 (11.3)

a) Geometric mean (CV%), b) Median (minimum to maximum)

The ratios of geometric least squares mean C_{max} and $AUC_{0\text{-inf}}$ of 4-mg tablet to 1-mg tablet in the fasted state were both approximately 0.9 and the corresponding 90% confidence intervals (CIs) were within the predefined bioequivalence criteria of 80% to 125%, indicating that the bioavailability of 4-mg tablet is comparable to that of 1-mg tablet.

The ratios of geometric least squares mean C_{max} and $AUC_{0\text{-inf}}$ of 4-mg tablet in the fed state to those in the fasted state were both approximately 0.9 and the corresponding 90% CIs were within the predefined bioequivalence criteria of 80% to 125%, indicating that food intake had no effect on the PK of 4-mg tablet.

Safety Results:

Only 1 case of alanine aminotransferase (ALT) increased was reported as an AE in 1 of 15 subjects (6.7%). This ALT increased was mild, did not cause any symptoms, returned to normal without any treatments, and was considered not related to the study drug. No deaths, serious adverse events (SAEs), or AEs leading to discontinuation occurred in all treatment groups. No abnormal ECG findings or abnormal changes in vital signs or laboratory tests were found. Therefore, S-888711 was safe and well-tolerated at a single dose of 4 mg in healthy male subjects.

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Conclusions:

- Bioavailability of 4-mg tablet was comparable to that of 1-mg tablet.
- Food intake had no effect on the PK of 4-mg tablet.
- S-888711 was safe and well-tolerated at a single dose of 4 mg in healthy male subjects.

Date of the Report: October 15, 2013