

2. Synopsis

English Translation (The original report was written in Japanese)

| Name of Sponsor: Shionogi & Co., Ltd. | Individual Study Table Referring to Part of the Dossier Volume: Page: | (For National Authority Use Only) | | | | | | | | | |
|---|--|-----------------------------------|--------|--------------|---------------|---|---------------------|-----------------------|---|-----------------------|---------------------|
| Name of Finished Product: Not determined | | | | | | | | | | | |
| Name of Active Ingredient: S-888711 | | | | | | | | | | | |
| Title of Study: A Pharmacokinetics Study of S-888711 in Caucasian Healthy Adult Male Subjects | | | | | | | | | | | |
| Investigator: [REDACTED] | | | | | | | | | | | |
| Study Center: [REDACTED] | | | | | | | | | | | |
| Publication: None | | | | | | | | | | | |
| Study Period: Three months From November [REDACTED], 2008 (date of study drug administration to the first enrolled subject) To January [REDACTED], 2009 (date of final observation for the last enrolled subject) | | | | | | | | | | | |
| Phase of Development: Phase 1 study | | | | | | | | | | | |
| Objectives: To investigate the pharmacokinetics of S-888711 following a single oral administration in healthy Caucasian adult male volunteers. | | | | | | | | | | | |
| Methodology: The present study was conducted to investigate the pharmacokinetics and safety after single oral doses of S-888711 by 3 methods as described below in healthy Caucasian adult male subjects. (1) 2-mg group (Part A) A single dose of 2-mg tablet was to be administered postprandially to 8 subjects. The duration of hospitalization was 8 days and 7 nights. Each subject received the study drug after breakfast on the next day of hospitalization. Each subject was discharged after examination on Day 7 (seventh day after administration), and the study-completion assessment was carried out on Day 10. (2) 0.25-mg crossover group (Part B) Ten subjects were divided into 2 groups consisting of 5 subjects each and a single dose of 0.25-mg tablet or a single dose of 0.25-mg solution was administered postprandially to subjects in each group in the respective periods according to the following sequence. <table border="1" data-bbox="500 1507 1117 1612"><thead><tr><th>Cohort</th><th>First period</th><th>Second period</th></tr></thead><tbody><tr><td>1</td><td>0.25-mg tablet (B1)</td><td>0.25-mg solution (B2)</td></tr><tr><td>2</td><td>0.25-mg solution (B2)</td><td>0.25-mg tablet (B1)</td></tr></tbody></table> Each subject received the study drug after breakfast on the next day of hospitalization in the first period and underwent the study-completion assessment at Day 7 in the first period. The administration in the second period was then performed on the next day of the study-completion assessment in the first period. Each subject was discharged after the study-completion assessment at Day 7 in the second period. (3) 0.1-mg crossover group (Part C) | | | Cohort | First period | Second period | 1 | 0.25-mg tablet (B1) | 0.25-mg solution (B2) | 2 | 0.25-mg solution (B2) | 0.25-mg tablet (B1) |
| Cohort | First period | Second period | | | | | | | | | |
| 1 | 0.25-mg tablet (B1) | 0.25-mg solution (B2) | | | | | | | | | |
| 2 | 0.25-mg solution (B2) | 0.25-mg tablet (B1) | | | | | | | | | |

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Ten subjects were be divided into 2 groups consisting of 5 subjects each and a single dose of 0.1-mg tablet or a single dose of 0.1-mg solution is to be administered postprandially to subjects in each group in the respective periods according to the following sequence. The study schedule was the same as in the-0.25 mg crossover group.

| Cohort | First period | Second period |
|--------|----------------------|----------------------|
| 1 | 0.1-mg tablet (C1) | 0.1-mg solution (C2) |
| 2 | 0.1-mg solution (C2) | 0.1-mg tablet (C1) |

Study Schedule for 2-mg group

| | Screening | Hospitalization | | | | | | | | | Study-completion | Discontinuation | |
|--|-----------|--------------------|--------------------|---------------------|-------|-------|-------|-------|-------|-------|------------------|-----------------|---|
| | | Day -1 (Admission) | Day 1 (Pre-dosing) | Day 1 (Post-dosing) | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 10 | | |
| Informed consent | X | | | | | | | | | | | | |
| Background factors | X | X | | | | | | | | | | | |
| Confirmation of the inclusion and exclusion criteria | X | X | X | | | | | | | | | | |
| Symptoms and signs | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Immunological tests | X | | | | | | | | | | | | |
| Urine screening tests for drug abuse | X | X | | | | | | | | | | | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Electrocardiogram | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology tests ^(a) | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood chemistry tests | X | X | X | | X | | X | | | X | X | X | X |
| Urinalysis | X | X | X | | X | | X | | | X | X | X | X |
| Blood collection for plasma drug concentration | | | X | X | X | X | X | X | X | X | | | |

(a) Prothrombin time (PT) and activated partial thromboplastin time (APTT) were measured at screening, 2 hours before and 4 hours after administration on Day 1, on Day 7 and at discontinuation. At 4 hours after administration, PT and APTT were only measured.

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Study schedule for the crossover groups

| | Screening | Hospitalization (Repeat this schedule for first to second period.) | | | | | | | | | Discontinuation |
|--|-----------|--|--------------------|---------------------|-------|-------|-------|-------|-------|---|-----------------|
| | | Day of admission (the day before administration) | Day 1 (Pre-dosing) | Day 1 (Post-dosing) | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 ^(b) (Study-completion) | |
| Informed consent | X | | | | | | | | | | |
| Background factors | X | X | | | | | | | | | |
| Confirmation of the inclusion and exclusion criteria | X | X | X | | | | | | | | |
| Symptoms and signs | X | X | X | X | X | X | X | X | X | X | X |
| Immunological tests | X | | | | | | | | | | |
| Urine screening tests for drug abuse | X | X | | | | | | | | | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X |
| Electrocardiogram | X | X | X | X | X | X | X | X | X | X | X |
| Hematology tests ^(a) | X | X | X | X | X | X | X | X | X | X | X |
| Blood biochemistry tests | X | X | X | | X | | X | | | X | X |
| Urinalysis | X | X | X | | X | | X | | | X | X |
| Blood collection of plasma drug concentration | | | X | X | X | X | X | X | X | X | |

(a) Prothrombin time (PT) and activated partial thromboplastin time (APTT) were measured at screening, 2 hours before and 4 hours after administration on Day 1, on Day 7 and at discontinuation. At 4 hours after administration, PT and APTT were only measured.

(b) Study-completion assessment in the first period served as predosing assessment in the second period.

Number of Subjects:

- Target number of subjects, 28; number of subjects randomized, 28; number of subjects administered, 28 (2-mg group, 8 subjects; 0.25-mg crossover group, 10 subjects; 0.1 mg crossover group, 10 subjects).
- Number of subjects in the pharmacokinetic analysis set, 28; number of subjects in the safety analysis set, 28 (2 mg group, 8 subjects; 0.25 mg crossover group, 10 subjects; 0.1 mg crossover group, 10 subjects).

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria

- (1) The subject must have a signed informed consent, be of their own free will and volition, before they are allowed to participate in the screening examinations.
- (2) The subject is between the ages of ≥ 20 and < 45 (at the time of agreement to the informed consent).
- (3) Caucasian (both parents are Caucasian) subjects living in Japan. The subject has either Japanese nationality, or has been issued and possesses a valid Certificate of Alien Registration.

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| <p>(4) The male subject who is judged as healthy during the screening examination by the (sub-) investigator.</p> <p>(5) Body mass index (BMI) is ≥ 18.5 to < 30.0 (kg/m²)</p> <p>(6) The number of platelets is within the standard reference range and is 300,000/μL or less.</p> <p>2. Exclusion criteria</p> <p>(1) The subject who has used a pharmaceutical product (prescription drugs, over-the-counter drugs, Chinese herbal medicines, dietary supplements/vitamins etc) within three days prior to the screening examinations.</p> <p>(2) The subject who has smoked or used nicotine-containing products (stop-smoking aids), within 24 weeks prior to the screening examinations.</p> <p>(3) The subject who has a history of use of cytochrome P450 inhibitors (eg, itraconazole) or inducers (eg, rifampicin) within 4 weeks prior to screening.</p> <p>(4) The subject who has a history of use of platelet-aggregation inhibitors within 4 weeks prior to screening. (Examples of platelet-aggregation inhibitors are the following: nonsteroidal anti-inflammatory drugs [eg, aspirin], coronary artery 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]).</p> <p>(5) The subject who has a history of use of thrombocytopenia inducing drugs (eg, quinidine, valproic acid) within 4 weeks prior to screening.</p> <p>(6) The subject who has a history of cardiac disorder or abnormal finding on electrocardiogram and is judged as ineligible by the (sub-) investigator.</p> <p>(7) The subject who has chronic disease and requires medication and other treatment, such as dietary restriction and physical therapy.</p> <p>(8) The subject who has a history of anaphylaxis or significant side effect to any drug.</p> <p>(9) The subject who has a current or past history of allergic symptoms including food allergy but excluding inactive pollen disease.</p> <p>(10) The subject who has a history of addiction to alcohol or drug.</p> <p>(11) The subject who has a positive urine on the screening of drug abuse.</p> <p>(12) The subject who has a history of nervous, gastric, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, hematic and other clinically important disorder and is judged as ineligible by the (sub-) investigator. Additionally the subject with a familial medical history of thrombosis, coagulation system disorder or thrombocytosis.</p> <p>(13) The subject with a medical history of stomach, vagal nerve or intestinal resection surgery (excluding appendectomy).</p> <p>(14) The subject who has donated more than 400 mL of blood within 12 weeks or more than 200 mL of blood within 4 weeks prior to screening.</p> <p>(15) The subject who has a hemorrhagic tendency.</p> | | |

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| (16) The subject who has received other study drugs within 16 weeks prior to the first dose of study medication. (17) The subject who refuses to obey items listed in “7. Control of Subjects” in this protocol. (18) The subject who has positive test results for serologic test for syphilis (lipid antibody, <i>Treponema pallidum</i> antibody), Hepatitis B surface antigen, Hepatitis C virus antibody, Human immunodeficiency virus antibody. (19) The subject who has received S-888711 before. (20) The subject who is judged as ineligible for this study by the (sub-) investigator due to other reasons. | | |
| Test Drug, Dose and Mode of Administration, Lot Number: 1. Test Drug (S-888711) S-888711 tablet (0.1 mg, 0.25 mg, 2 mg) or S-888711-containing solution formulation. 2. Dose <ul style="list-style-type: none"> • 2-mg group: 2 mg of S-888711 in tablet form. • 0.25-mg crossover group: 0.25 mg of S-888711 in tablet or solution form. • 0.1-mg crossover group: 0.1 mg of S-888711 in tablet or solution form. 3. Method of Administration <ul style="list-style-type: none"> • S-888711 tablet (0.1 mg, 0.25 mg, or 2 mg): Single oral administration after breakfast with 240 mL of water for injection. • S-888711 solution (0.1 mg or 0.25 mg): Single oral administration after breakfast with 20 mL of diluent solution for preparing S-888711 solution and 200 mL (100 mL × 2) of water for injection. 4. Lot Number (Manufacturing Number) S-888711 2 mg tablet, [REDACTED]; S-888711 0.25 mg tablet, [REDACTED]; S-888711 0.1 mg tablet, [REDACTED]; S-888711 bulk drug, [REDACTED]. | | |
| Control Drug, Dose and Mode of Administration, Lot Number: No control drug was used in the study. | | |
| Duration of Administration: One day (In the crossover groups, 2 days per subject, since the study drug of administration was conducted twice). | | |
| Criteria for Evaluation: 1. Pharmacokinetic Evaluation Based on plasma concentrations of unchanged S-888711 and its enantiomer, the following pharmacokinetic parameters (PK parameters) were calculated and evaluated for each method of administration and for each subject: maximum plasma concentration (C _{max}), time to reach C _{max} (T _{max}), area under the plasma concentration-time curve (AUC), terminal elimination half-life (t _{1/2,z}), apparent total clearance (CL/F), and mean residence time (MRT _{inf}). | | |

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| <p>2. Safety Evaluation</p> <p>The following safety variables were used for evaluation:</p> <ol style="list-style-type: none"> (1) Symptoms and signs (2) Adverse events (AEs) (3) Presence or absence of abnormal change from baseline in laboratory test values (hematology and blood chemistry tests, and urinalysis) (4) Presence or absence of abnormal change from baseline in physiological test values (blood pressure, pulse rate, respiratory rate, body temperature, and electrocardiogram parameters). | | |
| <p>Statistical Methods:</p> <p>1. Pharmacokinetics Analysis</p> <p>For plasma concentration measurements of unchanged S-888711 and its enantiomer, the arithmetic mean and its standard deviation (SD) and coefficient of variation (CV), geometric mean and its CV, median, minimum, and maximum were calculated in each subject and each method of administration. Each PK parameter was calculated based on the plasma concentrations of unchanged S-888711 and its enantiomer in each subject. For the PK parameters except for Tmax, the arithmetic mean and its SD and CV, geometric mean and its CV, median, minimum, and maximum were calculated. For Tmax, the arithmetic mean and its SD and CV, median, minimum, and maximum were calculated. Plasma concentration-time curves, the results of pharmacokinetic analysis, etc. were plotted if required.</p> <p>For each PK parameter obtained in the crossover group, analysis of variance was performed with consideration of cohort effect and period effect to compare between the formulations (tablet vs. solution). The other analyses were performed if required.</p> <p>2. Safety Analysis</p> <p>(1) Adverse events and adverse drug reactions</p> <p>The numbers of subjects with AE and adverse drug reaction (ADR) and the numbers of AEs and ADRs were counted for each method of administration; the incidences of AEs and ADRs (the percentages of subjects with AE and ADR) among all evaluable subjects. Their 95% confidence intervals were calculated by the Clopper-Pearson method.</p> <p>The numbers of subjects with AE and ADR and the numbers of AEs and ADRs were also counted according to the System Organ Class and Preferred Term. The numbers of subjects in each category regarding the date of onset, time to onset, action with the study drug, treatment given (except for actions with the study drug) severity, seriousness, outcome, and causal relationship with the study drug were also counted and analyzed for each method of administration.</p> <p>(2) Laboratory values and physiological values</p> <p>For quantitative data, the descriptive statistics (N, mean, SD, minimum, median, and</p> | | |

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maximum) in each method of administration were calculated. For qualitative data, the frequency of data in each category at each time point was summarized. The frequencies of abnormal values were also counted.

Summary - Conclusions

Pharmacokinetic Results:

The pharmacokinetics of S-888711 after a single oral dose of 2 mg tablet in the fed state in Caucasian subjects was assessed in comparison with the those of Japanese obtained previously in the comparative bioavailability of 2-mg tablet and food effect study (Study 0801M0612). Geometric mean C_{max}, AUC_{last}, and AUC_{inf} values of the 2-mg S-888711 tablet in Caucasian subjects were similar to those observed in Japanese subjects (Study 0801M0612), indicating that plasma S-888711 exposure in Caucasian subjects was comparable to that in Japanese subjects. PK parameters of S-888711 other than the C_{max}, AUC_{last}, and AUC_{inf} values were also similar between Caucasian and Japanese subjects.

In the 0.1- and 0.25-mg crossover groups, the pharmacokinetics of S-888711 was compared between tablet and solution formulations. Ratios of the geometric mean AUC_{inf} values in the S-888711 tablet to those in solution formulation were 0.822 for 0.1-mg tablet and 0.820 for 0.25-mg tablet; the bioavailability of the 0.1-mg tablet and 0.25-mg tablet was approximately 82% of the corresponding solution.

The plasma concentration of (+)-S-888711 determined only in the 2-mg group, an enantiomer of S-888711, was below the lower limit of quantification.

Pharmacokinetic parameters of unchanged S-888711

| Treatment group | N | C _{max} (µg/mL) | T _{max} ^(a) (hr) | AUC _{last} (µg·hr/mL) | AUC _{inf} (µg·hr/mL) | t _{1/2,z} (hr) | CL/F (L/hr) | MRT _{inf} (hr) |
|------------------|----|-----------------------------|---|-----------------------------------|----------------------------------|----------------------------|-----------------|----------------------------|
| 2 mg tablet | 8 | 0.0850 (12.9) | 5.0 (4.0-6.0) | 2.20 (13.2) | 2.26 (13.7) | 29.1 (20.0) | 0.886 (13.9) | 33.2 (14.5) |
| 0.1 mg tablet | 10 | 0.00219 (19.3) | 5.0 (4.0-6.0) | 0.0594 (21.6) | 0.0646 (20.7) | 24.8 (15.4) | 1.55 (20.6) | 34.6 (14.5) |
| 0.1 mg solution | 10 | 0.00243 (14.8) | 5.5 (5.0-12.0) | 0.0741 (24.3) | 0.0786 (23.5) | 24.7 (11.7) | 1.27 (23.5) | 36.0 (11.9) |
| 0.25 mg tablet | 10 | 0.00660 (12.5) | 5.5 (4.0-10.0) | 0.194 (17.6) | 0.201 (17.7) | 29.5 (25.2) | 1.24 (17.6) | 36.6 (12.8) |
| 0.25 mg solution | 10 | 0.00749 (9.6) | 6.0 (5.0-12.0) | 0.238 (15.5) | 0.245 (16.0) | 31.3 (19.0) | 1.02 (16.0) | 37.6 (11.6) |

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

(Source: Pharmacokinetic Study Report Table 9)

Safety Results:

One AE was reported in 1 of 28 subjects. The AE occurred in 1 of 8 subjects in the 2-mg group. No AEs were reported in either formulation (tablet and solution) of the 0.1- and 0.25-mg crossover groups. The AE reported in the study was considered unrelated to the study drug, and no ADR was hence reported in the study.

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| Acute tonsillitis reported as a mild AE had recovered during the study period. No abnormal changes or findings were found in laboratory parameters, ECG or vital signs. No deaths, serious AEs, or AEs leading to discontinuation occurred. | | |
| Conclusions: The pharmacokinetics, safety and tolerability in healthy Caucasian adult male subjects living in Japan after S-888711 single oral dose of 0.1 or 0.25 mg S-888711 in tablet or solution form in the fed state were evaluated as follows: <ul style="list-style-type: none">• The pharmacokinetics of S-888711 following a single oral dose of 2-mg tablet appeared comparable for Caucasian and Japanese subjects.• The bioavailability of the 0.1- tablet and 0.25-mg tablet was approximately 82% of the corresponding solution formulations.• The oral dosing of S-888711 was safe and well-tolerated over the dose range of 0.1 to 2 mg. | | |
| Date of the Report: 27 May 2009 | | |
| Date of Amendment 1: 16 Nov 2017 | | |