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**	(For National Authority Use Only)
Name of Finished Product: Not determined	**Volume:**	
Name of Active Ingredient: S-888711	**Page:**	

Title of Study: Phase I multiple-dose, dose-ranging, double-blind, placebo-controlled study to assess the safety and pharmacokinetics of S-888711 in healthy adult male subjects

Investigator: [redacted]

Study Center: [redacted]

Publication: None

Study Period: Five months
From May [redacted], 2008 (date of study-drug administration to the first subject)
To September [redacted], 2008 (date of final observation for the last subject)

Phase of Development: 1

Objectives: To determine the safety, tolerability, and pharmacokinetics of multiple oral doses of S-888711 in healthy adult male subjects.

Methodology:

Study Schedule

	Screening	Admission	Administration period														
			Day 1														
		The day before admini-stration	Pre-dosing	Post-dosing	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Informed consent	X																
Background factors	X	X															
Immunological tests	X																
Drug abuse screening urine tests	X	X															
Confirmation of the inclusion and exclusion criteria	X	X	X														
Study drug administration				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event				←													
Symptoms and signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X	X	X				X			X			X			
Hematology tests (excluding PT and APTT)	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology tests (PT and APTT only)	X	X	X								X						
Biochemical tests	X	X	X		X			X			X			X			
Endocrinological tests			X								X						
Urinalysis	X	X	X		X			X			X			X			
Platelet aggregation	X	X	X								X						
Blood sampling for measurement of plasma drug concentration			X	X	X	X	X	X	X	X	X		X				X
Sampling for urine drug concentration measurement[a)]		←															

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Study Schedule (continued)

	Follow-up period														Visit	At dis-contin-uation
	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28 Dis-charge	Day 35 Post-exam	
Study drug administration																
Adverse event	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Symptoms and signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X			X			X			X				X		X
Hematological tests (excluding PT and APTT)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology tests (PT and APTT only)	X						X							X	X	X
Biochemical tests	X			X			X			X				X	X	X
Endocrinological tests	X						X							X		X
Urinalysis	X			X			X			X				X	X	X
Platelet aggregation	X						X							X	X	X
Blood sampling for measurement of plasma drug concentration	X	X	X	X	X	X										
Sampling for urine drug concentration measurement[a)]	→	→	→	→	→	→										

a) Urine is collected at the following timepoints→ Day 1 (prior to initial dosing), Days 1 to 14 (0 to 24 hours after daily dosing), Days 15 to 19 (24 to 48, 48 to 72, 72 to 96, 96 to 120, and 120 to 144 hours after final dosing.)

S-888711 2 mg tablet, 0.5 mg solution, or 0.25 mg solution was orally administered to healthy adult male subjects once daily for 14 days to investigate its safety, tolerability and pharmacokinetics.

The study was conducted in 8 subjects at each dose level; the 6 subjects were randomly allocated to active S-888711 and 2 subjects were randomly allocated to placebo.

The treatment groups were designed with the dose-escalation sequence of Step 1 (2 mg) → Step 2 (4 mg) → Step 3 (6 mg). Extra Steps A to C were also established as substitute dose levels in case that it was judged inappropriate to proceed to the next higher dose level. Actually, since it was judged inappropriate to proceed from Step 1 to Step 2, this study was conducted with sequence of Step 1 (2 mg) → Extra Step A (0.5 mg) → Extra Step C (0.25 mg).

The hospitalization period was for 29 days and 28 nights at each treatment group. Multiple dosing was performed for 14 days from the next day of hospitalization. Examination at the time of discharge was performed on Day 28 (28th day after the initial

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dosing) and the post examination on Day 35 (35th day after the initial dosing).

Number of Subjects:
Target number of subjects: 24
Number of subjects randomized: 24
Number of subjects administered: 18 in the S-888711 groups; 6 in the placebo group
Number of subjects in the pharmacokinetic analysis set: 18 (6 each in the 0.25 mg, 0.5 mg, and 2 mg groups)
Number of subjects in the safety analysis set: 24 (18 in the S-888711 groups; 6 in the placebo group)

Diagnosis and Criteria

1. Inclusion criteria

(1) A signed and dated written informed consent is obtained from the subject who voluntarily participates in this study prior to screening.
(2) Subject is between the ages of ≥20 and <40 (at the timing of agreement to the informed consent).
(3) The male subject is judged as healthy during the screening examination by the (sub-) investigator.
(4) Body weight of ≥50 to ≤80 kg and body mass index (BMI) of ≥18.5 to <25.0 (kg/m^2).
(5) The number of platelets is within the normal range and is 300,000/μL or less.

2. Exclusion criteria

(1) The subject who used prescription or non-prescription drugs, including Chinese herbal medicine, dietary supplements and vitamins etc., within 3 days prior to screening.
(2) The subject who smoked tobacco or used nicotine-containing products within 24 weeks prior to screening.
(3) The subject who used cytochrome P450 inhibitors (eg, itraconazole) or inducers (eg, rifampicin) within 4 weeks prior to screening.
(4) The subject who used platelet aggregation inhibitors (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]) within 4 weeks prior to screening examination.
(5) The subject who has less than 70% of maximum platelet aggregation rate induced by ADP and collagen each as an agonist in the platelet aggregation test at screening.
(6) The subject who used thrombocytopenia-inducing drug (eg, quinidine, valproic acid) within 4 weeks prior to screening.
(7) The subject who has a history of heart disease or abnormal finding on ECG and is judged as ineligible by the (sub-) investigator
(8) The subject who has chronic disease and requires medication and other treatment,

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such as dietary restriction and physical therapy.

(9) The subject who has a history of anaphylaxis or serious adverse drug reaction suspected to be induced by a drug.

(10) The subject with allergic symptoms including food allergy but excluding inactive pollen disease, or a history thereof.

(11) The subject who has a history of addiction to alcohol or drug.

(12) The subject who has positive urine on the screening of drug abuse.

(13) The subject with nervous, gastric, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, hematologic and other clinically important disorder, or a history thereof, and is judged as ineligible by the (sub-) investigator. The subject whose family has a history of thrombosis/coagulation system disorder or thrombocytosis.

(14) The subject who has a history of an operation, such as gastrectomy, vagotomy and enterectomy except for appendectomy.

(15) 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.

(16) The subject who has a hemorrhagic tendency.

(17) The subject who has received other study drugs within 16 weeks prior to the first dose of study medication.

(18) The subject who can not obey items listed in "7. Control of Subjects" in the protocol.

(19) The subject who has positive test results for serologic test for syphilis (lipid/TP antibody), Hepatitis B surface antigen, Hepatitis C virus antibody or human immunodeficiency virus antibody.

(20) The subject who has received S-888711 before.

(21) 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 2 mg tablet and S-888711 solution

2. Dosage

2 mg group: One S-888711 2 mg tablet
0.5 mg group: Solution containing 0.5 mg of S-888711 (10 g solution [approximately 10 mL] per dose)
0.25 mg group: Solution containing 0.25 mg of S-888711 (5 g solution [approximately 5 mL] per dose)

3. Mode of Administration

2 mg group: Orally administered with 240 mL of water for injection once daily after breakfast for 14 days
0.5 mg and 0.25 mg groups: Orally administered with 20 mL of diluent solution for

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preparing S-888711 solution and 200 mL (100 mL × 2) of water for injection once daily after breakfast for 14 days

4. Lot Number (Manufacturing Number)
S-888711 bulk drug: [redacted]
S-888711 2 mg tablet: [redacted]

Control Drug, Dose and Mode of Administration, Lot Number:
1. Control drug
Placebo tablet (PLACEBO-A) for S-888711 (hereinafter S-888711 placebo tablet) and S-888711 placebo solution

2. Dosage
2 mg group: One S-888711 placebo tablet
0.5 mg group: S-888711 placebo solution (10 g solution [approximately 10 mL] per dose)
0.25 mg group: S-888711 placebo solution (5 g solution [approximately 5 mL] per dose)

3. Mode of Administration
2 mg group: Orally administered with 240 mL of water for injection once daily after breakfast for 14 days.
0.5 mg and 0.25 mg groups: Orally administered with 20 mL of diluent solution for preparing S-888711 solution and 200 mL (100 mL × 2) of water for injection once daily after breakfast for 14 days.

4. Lot Number (Manufacturing Number)
S-888711 placebo tablet: [redacted]

Duration of Administration: Given once daily for 14 days

Criteria for Evaluation:
1. Pharmacokinetic Evaluation
Based on plasma and urinary concentrations of S-888711 and its enantiomer measured for the initial dosing (Day 1) and Days 7 and 14, the following pharmacokinetic parameters (PK parameters) in each group and each subject were calculated for evaluation of pharmacokinetic profiles following multiple dosing orally: Maximum plasma concentration (Cmax), time to reach Cmax (Tmax), area under the plasma concentration-time curve (AUC_{0-24hr} and AUC_{inf}), elimination half-life ($t_{1/2,\ 24hr}$ and $t_{1/2,\ z}$), apparent total clearance (CL/F), Cmax and AUC_{0-24hr} accumulation ratios during multiple dosing (R_{Cmax} and R_{AUC}), and urinary excretion ratio (Ur and Ur, total).

2. Safety Evaluation
The following safety items were used for evaluation.
(1) Subjective symptoms and objective findings
(2) Adverse events (AEs)

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(3) Change from baseline in laboratory test values (hematology tests, blood biochemical tests, endocrinological tests, urinalysis, and platelet aggregation tests)
(4) Change from baseline in physiological test values (blood pressure, pulse rate, respiratory rate, body temperature, and ECG parameters)

Statistical Methods:

1. Pharmacokinetics Analysis

For plasma concentration measurements of S-888711 and its enantiomer, the arithmetic mean and its standard deviation (SD) and coefficient of variation (CV), geometric mean (GeoMean) and its CV (GeoCV), median, minimum, and maximum were calculated in each group and each time point. In addition, based on plasma and urinary concentrations of S-888711, the PK parameters on the initial dosing (Day 1) and Days 7 and 14 were calculated for each subject. For each PK parameter on Days 1, 7 and 14, the arithmetic mean and its SD and CV, GeoMean and GeoCV, median, minimum, and maximum were calculated for each group, and the PK parameters were compared among the treatment groups by analysis of variance as required. The plasma concentration-time profile, urinary excretion ratio, and pharmacokinetic results, etc. were plotted as required.

2. Safety Analysis

(1) Adverse events and adverse drug reactions

The numbers of subjects with AE and adverse drug reaction (ADR) and the numbers of AEs and ADRs were counted for each group to calculate the incidences of AE and ADR (the percentages of subjects with AE and ADR) among all evaluable subjects. Their 95% confidence intervals were calculated by the Clopper-Pearson method. The numbers of subjects with AE and ADR and the numbers of AEs and ADRs were counted according to System Organ Class and Preferred Term for each group. The numbers of subjects in each category regarding the date of onset, severity, action with the study drugs, treatment given (except for actions with the study drug,) seriousness, outcome, and causal relationship with the study drug were also counted and analyzed for each group.

(2) Laboratory values and physiological values

The descriptive statistics (N, mean, SD, minimum, median, and maximum) for quantitative data obtained at each time point were calculated for each group. For qualitative data, the frequency of each category at each time point was summarized. The frequencies of abnormal values and abnormal changes were also counted.

Summary − Conclusions

Pharmacokinetic Results:

Multiple oral doses of 0.25 mg (solution), 0.5 mg (solution), and 2 mg (tablet) of S-888711 were administered once daily after breakfast for 14 days to Japanese healthy adult male subjects. Increases in Cmax and AUC_{0-24hr} values appeared to be dose-proportional across the three dose range of 0.25 mg, 0.5 mg, and 2 mg on Days 1, 7, and 14, indicating linear pharmacokinetics. The $t_{1/2,24hr}$ values appeared to be almost the same across the dose

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range of 0.25 to 2 mg on Days 1, 7, and 14.

For the trough plasma concentration of S-888711, steady state appeared to be achieved on Day 5 in all dose groups. The accumulation ratios of Cmax and AUC_{0-24hr} values to Day 1 were approximately 2-fold on both Days 7 and 14 in all dose groups.

These results showed that the pharmacokinetics of S-888711 at multiple once daily oral doses of 0.25, 0.5, and 2 mg under fed conditions were linear across the dose range of 0.25 to 2 mg, with dose-proportional increase in plasma concentration of unchanged S-888711. The accumulation ratios of Cmax and AUC_{0-24hr} values on both Days 7 and 14 to Day 1 were approximately 2-fold, suggesting that accumulation of S-888711 occurred in the plasma following multiple dosing, but steady-state was reached on or before Day 7.

The plasma concentration of (+)-S-888711, an enantiomer of S-888711, was below the lower limit of quantification. Regarding urinary excretion, the urinary concentrations of S-888711 and (+)-S-888711 were below the lower limit of quantification.

Table PK parameters of S-888711 during multiple oral dosing (Once daily fed administration for 14 days)

Dose	Time point	No. of subjects	Cmax (μg/mL)	Tmax[a] (hr)	AUC_{0-24hr} (μg·hr/mL)	$t_{1/2,24hr}$ (hr)	R_{Cmax}[b]	R_{AUC}[b]
0.25 mg	Day 1	6	0.00848 (6.8)	8.0 (5.0-10.0)	0.135 (8.1)	26.6 (28.0)		
	Day 7	6	0.0197 (5.3)	8.0 (4.0-10.0)	0.333 (11.9)	28.1 (11.3)	2.32 (6.3)	2.47 (7.0)
	Day 14	6	0.0180 (11.7)	6.5 (4.0-10.0)	0.317 (13.0)	30.1 (22.6)	2.12 (10.4)	2.34 (8.7)
0.5 mg	Day 1	5	0.0192 (9.6)	8.0 (5.0-10.0)	0.327 (7.1)	24.7 (26.2)		
	Day 7	5	0.0349 (13.6)	8.0 (5.0-10.0)	0.657 (12.8)	32.0 (34.2)	1.81 (10.1)	2.01 (7.3)
	Day 14	5	0.0389 (13.7)	6.0 (4.0-6.0)	0.703 (10.4)	23.8 (21.2)	2.03 (13.5)	2.15 (7.2)
2 mg	Day 1	6	0.0783 (16.7)	4.0 (4.0-10.0)	1.28 (12.3)	23.1 (19.6)		
	Day 7	6	0.159 (16.6)	4.0 (4.0-10.0)	2.67 (12.6)	27.8 (39.8)	2.03 (7.1)	2.09 (5.7)
	Day 14	5	0.156 (5.7)	4.0 (4.0-4.0)	2.63 (8.1)	29.3 (26.8)	2.11 (7.5)	2.13 (11.0)

GeoMean (%CV).
a) Median (min to max), b) Ratio of Cmax or AUC_{0-24hr} value to Day 1

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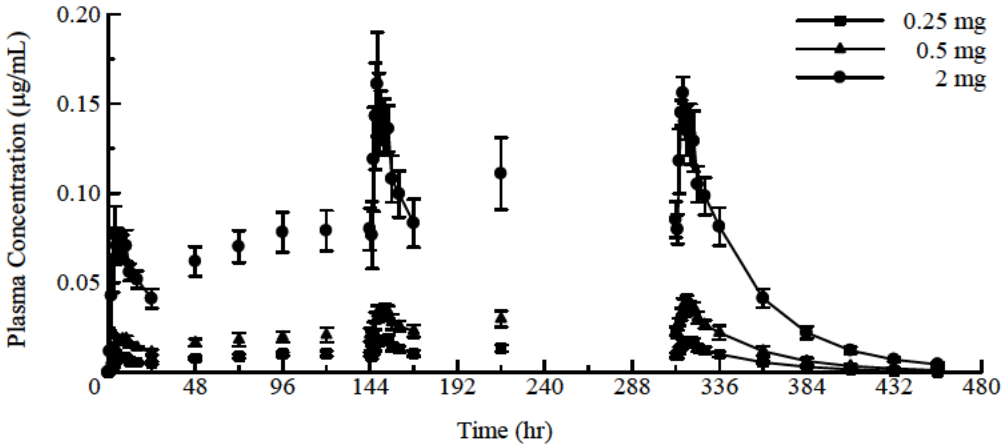

(Mean ± SD, N=6 except for N=5 on and after Day 2 in the 0.5 mg group and on and after Day 14 in the 2 mg group)

Figure Mean plasma concentration-time curves of unchanged S-888711 during multiple oral dosing (Once daily fed administration for 14 days)

Safety Results:

The study evaluated the safety and tolerability at multiple once daily doses of 2 mg tablet, 0.5 mg solution, and 0.25 mg solution after breakfast for 14 days in healthy adult male subjects. A total of 10 AEs were reported in 10 of 18 subjects in the S-888711 groups (6 AEs in 6 of 6 subjects in the 2 mg group; 3 AEs in 3 of 6 subjects in the 0.5 mg group; and 1 AE in 1 of 6 subjects in the 0.25 mg group.) Three AEs were reported in 2 of 6 subjects in the placebo group. All AEs in the S-888711 groups were handled as ADRs.

The AEs reported were as follows: 6 events (N=6) of platelet count increased in the 2 mg group; gastroenteritis, 1 event each (N=1 each) of platelet count increased, and blood corticotrophin increased in the 0.5 mg group; 1 event (N=1) of ALT increased in the 0.25 mg group; and 1 event each (N=1 each) of arthropod sting, ALT increased, and AST increased in the placebo group.

The events of platelet count increased were abnormal changes considered to be due to the pharmacological action of S-888711; the incidence of platelet count increased had a tendency to increase with an increase in the dose of S-888711. For other AEs and parameters values, neither their incidences nor the magnitudes of changes were increased with the increasing doses of S-888711.

Endocrinological testing was performed to examine the toxic finding of S-888711 on the adrenal cortex which was observed in nonclinical studies. No change suggestive of adrenocortical dysfunction was observed in this study.

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After a single dose of S-888711 of 1 to 50 mg in healthy adult subjects in the single dose study (Study 0713M0611), AEs reported in the S-888711 groups were C-reactive protein increased, blood creatine phosphokinase increased, eosinophil percentage increased, and WBC count increased other than platelet count increased; none of these AEs occurred in the present study. In the comparative BA of 2 mg tablet and food effect study (Study 0801M0612), skin laceration, WBC count increased, neutrophil percentage increased, C-reactive protein increased, and urobilin urine present were observed; none of these AEs occurred in the present study.

All of the AEs reported in this study were assessed as mild in severity. The event of arthropod sting observed in the placebo group required follow-up investigation since it occurred just before the end of the study period. All other AEs were confirmed to have resolved during the study period. Neither deaths nor SAEs occurred, and neither abnormal ECG findings nor abnormal changes in vital sign were observed in this study.

The maximum platelet aggregation rate on Day 21 tended to decrease temporarily with increasing doses of S-888711; platelet aggregation ability was judged to be within the normal range in all subjects based on comprehensive evaluation in conjunction with platelet aggregation curve in each subject. However, a more thorough platelet aggregation test is needed to evaluate platelet aggregation in more detail.

These results indicated that multiple once daily oral doses of 0.25 mg or 0.5 mg S-888711 in solution form or 2 mg S-888711 in tablet form after breakfast for 14 days have good safety and tolerability profiles.

Conclusions:
The pharmacokinetics, safety and tolerability of S-888711 at multiple once daily oral doses of 0.25, 0.5, and 2 mg under fed conditions for 14 days were confirmed as follows:

- Increases in Cmax and AUC_{0-24hr} of S-888711 appeared to be dose-proportional across the dose range of 0.25 to 2 mg.
- The accumulation ratios of Cmax and AUC_{0-24hr} values on both Days 7 and 14 to Day 1 were approximately 2-fold.
- The steady state of plasma concentration of S-888711 appeared to be achieved on Day 5 in all dose groups.
- S-888711 was safe and well-tolerated across the dose range of 0.25 to 2 mg.

Date of the Report: 17 December 2008

Date of the Amendment 1: 16 Nov 2017