2. Synopsis

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 single-dose, double-blind, placebo-controlled study in healthy adult male subjects to assess the safety and pharmacokinetics of S-888711

Investigator: [redacted]

Study Center: [redacted]

Publication: None

Study Period: Five months
From October [redacted], 2007 (date of study-drug administration to the first enrolled subject)
To February [redacted], 2008 (date of final observation for the last enrolled subject)

Phase of Development: Phase I clinical study

Objects: To determine the safety, tolerability, and pharmacokinetics of single oral dose of S-888711 in healthy adult males in a placebo-controlled, randomized, double-blind design.

Methodology:

[Study Schedule]

	Screening	Hospitalization						Follow-up examination		Post examination
		Admission (the day before administ-ration)	Day 1 (Before administ-ration)	Day 1 (After administ-ration)	Day 2	Day 3	Day 4	Day 7	Day 10	Day 14
Informed consent	X									
Background factors	X	X								
Confirmation of the inclusion and exclusion criteria	X	X								
Subjective symptoms and objective findings	X	X	X	X	X	X	X	X	X	X
Adverse events				←	—	—	—	—	—	→
Immunological tests	X									
Drug abuse screening urine tests	X	X								
Vital signs	X	X	X	X	X	X	X	X	X	X
Hematology tests	X	X	X		X	X	X	X	X	X
Blood biochemistry tests	X		X		X	X	X	X	X	X
Endocrinology tests			X		X	X	X	X	X	X
Urinalysis	X		X		X	X	X			X
Platelet aggregation	X	X	X		X		X	X		X
ECG	X	X	X	X	X	X	X	X	X	X
Blood sampling for measurement of plasma drug concentration[a)]			X	X	X	X	X	X	X	X
Urine sampling for measurement of urine drug concentration[b)]		←	—	—	—	—	→			

a) In the Step III, IV, V, VI, VIII, samples for search for major metabolites will be obtained just before administration, and at 1, 4, 8, and 24 hours after administration.
b) In the Step III, IV, V, VI, VIII, samples for search for major metabolites will be collected separately for 0 to 6 hours, 6 to 12 hours, and 12 to 24 hours after administration.

S-888711 (1, 2, 4, 10, 25, or 50 mg) or placebo was administered as a single oral dose to healthy

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		

adult male subjects in the fasting state to investigate the safety, tolerability, and pharmacokinetics of S-888711. Administration was initiated with a dose of 1 mg of S-888711. While confirming the safety of subjects, the dose was escalated up to 50 mg stepwise. and the incidences of adverse events (AEs) /adverse drug reactions (ADRs) and pharmacokinetic parameters were investigated in the dose range of 1 to 50 mg. For 8 subjects at each dose level, 6 subjects were randomly allocated to S-888711 and 2 subjects were randomly allocated to placebo. The study period for each subject was from the day of admission (the day before study-drug administration) through post examination on Day 14. Each subject received the allocated study drug the day after admission and was hospitalized until Day 4. After discharge, follow-up examinations on Days 7 and 10 and post examination on Day 14 were conducted.
Although the higher dose levels of 75 mg and 100 mg were planned as next doses to 50 mg in the protocol, this study was completed with 50-mg administration, instead of proceeding to 75-mg administration, after deliberate evaluation of examination results observed in 50-mg administration.

Number of Subjects:
<Single-dose study>
Target number of subjects: 64
Number of subjects randomized: 47
Number of subjects administered: 36 in the S-888711 group and 11 in the placebo group
Number of subjects in the pharmacokinetic analysis set: 36 (n=6 each for 1, 2, 4, 10, 25, and 50 mg)
Number of subjects in the safety analysis set: 47 (n=36 in the S-888711 group and n=11 in the placebo group)

Diagnosis and main criteria for inclusion
1. Inclusion criteria
1) A signed and dated written informed consent is obtained from the subject who spontaneously 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 in screening examination by an 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 platelet is within the standard level and 300,000/μL or less.

2. Exclusion criteria
1) The use of prescription or non-prescription drugs, including Chinese herbal medicine, dietary supplements, within 3 days prior to screening.
2) The subject who has a history of regular use of tobacco or nicotine-containing products within 24 months prior to screening.
3) The subject who has a history of use of cytochromes-P450 inhibitor (e.g. itraconazole) or inducer (eg. rifampicin) within 4 weeks prior to screening.
4) The subject who has a history of use of platelet-aggregation inhibitor within 4 weeks prior to screening. (nonsteroidal anti-inflammatory drugs (e.g., aspirin), coronary vasodilators (e.g., dipyridamole), antihypertensive drugs (e.g., nifedipine), diuretics (e.g., furosemide), psychotropic drugs (e.g., chlorpromazine), prostaglandin preparations (e.g., Prostandin), antibiotics (e.g., penicillin), anticoagulant (e.g., heparin), or antiplatelet drugs (e.g., ticlopidine)
5) The subject who has less than 70% of platelet maximum aggregation rate induced by ADP and collagen each as an agonist in the platelet aggregation test in screening examination.

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		

6) The subject who has a history of use of thrombocytopenia inducing drug (eg. quinidine,valproic acid) within 4 weeks prior to screening.
7) The subject who has a history of cardiac episode, cardiac murmur or abnormal finding on electrocardiogram and is judged as an ineligible by the (sub-) investigator.
8) The subject who has chronic disease required medication and other treatment, such as dietary restriction and physical therapy.
9) The subject who has a history of anaphylaxis or serious side effect induced by a drug.
10) The subject who has a history of allergic symptoms including food allergy but excluding inactive pollen disease.
11) The subject who has a history of addiction of alcohol or drug.
12) The subject who has a positive urine on the screening of drug abuse.
13) The subject who has a history of nervous, gastric, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, hematic and other clinically important disorders and is judged as an ineligible by the (sub-) investigator. The subject whose family has a history of hematic disorder.
14) The subject who has a history of an operation, such as excision of stomach, vagal nerve and gut except for appendicectomy.
15) The subject who has donated 400 mL of blood within 12 weeks or excess of 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 investigational products 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 this protocol.
19) The subject who has positive test results for serologic test for syphilis, Hepatitis B surface antigen, Hepatitis C virus antibody or human immuno-deficient virus antibody.
20) The subject who is judged as an ineligible for this study by an investigator due to other reasons.

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

1. Test Drug (S-888711)

A solution formulation containing S-888711

2. Dosage and Administration

A solution formulation containing 1, 2, 4, 10, 25, or 50 mg of S-888711 was orally administered to subjects in the fasting state.

3. Mode of Administration

For six subjects assigned to receive S-888711 at each dose level, 20 g (approximately 20 mL) of S-888711 solution, which was prepared immediately before use, was administered as a single oral dose with rinse solutions (20 mL of solution for preparing of S-888711 solution and 200 mL of water for injection) to subjects in the fasting state.

4. Lot Number (Manufacturing Number)

S-888711 bulk material (for preparation of a solution formulation): [redacted]

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

1. Control Drug

A solution formulation containing placebo for S-888711

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:**	

2. Dosage and Administration
A placebo solution formulation was orally administered to subjects in the fasting state.

3. Mode of Administration
For two subjects assigned to receive placebo at each dose level, 20 g (approximately 20 mL) of placebo solution, which was prepared just before use, was administered as a single oral dose with rinse solutions (20 mL of solution for preparing S-888711 solution and 200 mL of water for injection) to subjects in the fasting state.

Duration of Administration: One day

Criteria for Evaluation:

1. Pharmacokinetic Evaluation
Based on measured plasma concentrations of S-888711 and its enantiomer, the maximum plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax), area under the plasma concentration-time curve (AUC), terminal elimination half-life ($t_{1/2,z}$), apparent total clearance (CL/F), and urinary excretion ratio (Ur) at each dose level and in each subject were calculated for evaluation.

2. Safety Evaluation
The following safety variables were used for evaluation.
1) Subjective symptoms and objective findings
2) AEs and ADRs
3) Presence or absence of abnormal change from baseline in laboratory test values (hematology, blood biochemical, and endocrinological 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 ECG parameters)
5) Presence or absence of abnormal change from baseline in platelet aggregation ability

Statistical Methods:

1. Pharmacokinetics Analysis
Based on plasma concentrations of S-888711 and its enantiomer measured up to 72 hr post dose, the pharmacokinetic (PK) parameters were calculated for each dose level and each subject. For each dose level, the arithmetic mean with its standard deviation (SD) and coefficient of variation (CV), geometric mean with its CV, median, minimum, and maximum were calculated for parameters other than Tmax. For Tmax, the arithmetic mean with its SD and CV, median, minimum, and maximum were calculated. Changes over time in plasma concentration, urinary excretion ratio, and results of PK analysis were plotted as appropriate. Regression analysis was performed to analyze relationships between dose and Cmax, AUC_{0-last}, and AUC_{inf} of S-888711 and examine the dose proportionality of PK parameters. The $t_{1/2,z}$ and CL/F values of S-888711 were compared among the dose groups by analysis of variance (ANOVA).

2. Safety Analysis

1) Adverse events and adverse drug reactions
The numbers of subjects with AE and ADR and the total numbers of AEs and ADRs were counted for each dose group, and the percentages of subjects with AE and ADR among all evaluable subjects, i.e., incidences of AEs and ADRs were calculated. The 95% confidence intervals for

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:**	

incidences were calculated by the Clopper-Pearson method. For each dose group, the numbers of subjects with AE and ADR and the total numbers of AEs and ADRs were tabulated according to System Organ Class and Preferred Term. The numbers of subjects in each category regarding date of onset, severity, measures taken other than action with the study drug, seriousness, outcome, and causal relationship with the study drug were tabulated and analyzed for each dose group.

2) Laboratory values, physiological values, and platelet aggregation ability

For parameters measured as continuous data, summary statistics (N, mean, SD, minimum, median, and maximum) at each observation time point were calculated for each dose group. For parameters measured as qualitative data, a 2×2 contingency table for baseline data vs. data at each observation time point was prepared and analyzed. The incidences of abnormal values and abnormal changes were also calculated and analyzed.

Summary − Conclusions

Pharmacokinetic Results:

The following PK parameters of unchanged S-888711 were obtained after a single oral dose of S-888711 solution in the fasting state: Tmax ranged from 3.5 to 4.0 hours post dose, while Cmax, AUC_{0-last}, and AUC_{inf} values increased in proportion to dose in the dose range of 1 to 50 mg. No dose-dependent changes were observed in either $t_{1/2,z}$ or CL/F in the dose range of 1 to 50 mg. These findings indicated the pharmacokinetic linearity of unchanged S-888711 in plasma.

Regarding urinary excretion, S-888711 was not detected in urine in the dose range of 1 to 50 mg.

For (+)-S-888711, an enantiomer of S-888711, on the other hand, the AUC_{inf} and Cmax values increased dose-dependently; however, plasma concentrations of (+)-S-888711 over time were much lower than those of unchanged S-888711, and the enantiomer-to-unchanged AUC_{inf} ratio ($Ratio_{AUC}$) was less than 0.003.

PK parameters after a single oral dose of S-888711 in the fasting state in each dose group

Dose group	N	Cmax[a] (μg/mL)	Tmax[b] (hr)	AUC_{0-last}[a] (μg·hr/mL)	AUC_{inf}[a] (μg·hr/mL)	$t_{1/2,z}$[a] (hr)	CL/F[a] (L/hr)
1 mg	6	0.0449 (29.1)	4.0 (3.5-4.0)	1.18 (21.1)	1.34 (21.5)	23.2 (17.8)	0.748 (21.4)
2 mg	6	0.0897 (15.8)	3.8 (3.5-4.0)	2.04 (15.4)	2.21 (16.0)	20.4 (7.9)	0.905 (15.9)
4 mg	6	0.213 (5.7)	3.8 (3.5-4.0)	4.84 (7.9)	5.29 (8.1)	20.5 (9.0)	0.757 (8.1)
10 mg	6	0.593 (16.0)	3.5 (3.5-4.0)	13.8 (16.2)	15.2 (17.1)	21.2 (9.1)	0.657 (17.1)
25 mg	6	1.23 (22.5)	4.0 (3.5-6.0)	26.4 (22.9)	28.3 (24.1)	19.3 (7.9)	0.883 (24.1)
50 mg	6	2.14 (16.3)	4.0 (3.5-6.0)	48.7 (17.8)	53.5 (19.5)	21.1 (19.4)	0.934 (19.4)

a) Geometric mean (%CV). b) Median (minimum − maximum)

[Source: Pharmacokinetic Study Report, Table 3 (a to f)]

Safety Results:

After S-888711 (1, 2, 4, 10, 25, or 50 mg) or placebo solution was administered as a single oral dose in the fasting state, a total of 13 AEs occurred in 10 subjects in the S-888711 groups [one event in one subject in the 1-mg group; one event in one subject in the 2-mg group; six events in four subjects in the 10-mg group; one event in one subject in the 25-mg group; and four events in three subjects in the 50-mg group], while one event occurred in one subject in the placebo group. All of these events were abnormal changes in laboratory values.

Specific AEs observed in the S-888711 groups included: two, one, and three events of Platelet count increased in the 10-mg, 25-mg, and 50-mg groups, respectively; two events each of C-reactive

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:**	

protein increased and Blood creatine phosphokinase increased in the 10-mg group; one event each of Eosinophil percentage increased in the 2-mg and 50-mg groups; and one event of White blood cell count increased in the 1-mg group. Among these events, the two events of Blood creatine phosphokinase increased were judged unrelated to S-888711, while the remaining 11 events observed in ten subjects were handled as ADRs.

The event of Platelet count increased is an abnormal laboratory change considered due to the pharmacological effect of S-888711, and in fact, the platelet count increased in proportion to dose of S-888711. However, no dose-dependent increase was observed in either the incidences of other AEs or the magnitude of change in other parameter values.

All AEs were assessed as mild in severity and were confirmed to have resolved without treatment by Day 28. Other than the above laboratory parameters, there were no AEs related to various examinations, subjective symptoms, or objective findings. No deaths or serious AEs occurred. It was confirmed that when administered as a single oral dose of 1 to 50 mg in a solution formulation, S-888711 has good safety and tolerability profiles.

Conclusions:

It was confirmed that when administered as a single oral dose of 1, 2, 4, 10, 25, or 50 mg in a solution formulation in the fasting state, S-888711 exhibits linear pharmacokinetics in the dose range of 1 to 50 mg, with good safety and tolerability profiles.

Date of the Report: May 28, 2008

Date of the Amendment 1: 16 Nov 2017