2. Synopsis

English Translation (The original report was written in Japanese)

Name of Sponsor: Shionogi & Co., Ltd. **Name of Finished Product:** Not 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 crossover study to investigate the relative bioavailability and the effect of food on the pharmacokinetics of a single dose of S-888711 in healthy male subjects

Investigator: [redacted]

Study Center: [redacted]

Publication: None

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

Phase of Development: Phase 1 clinical study

Objectives:

Primary objective

To compare pharmacokinetics of S-888711 (2 mg) solution* and tablet formulations in single oral dose administration to healthy adult males, and to investigate food effect on the pharmacokinetics of S-888711 in the tablet formulation.

Secondary objective

(1) To investigate pharmacokinetics of S-888711 (10 mg) tablet in single oral dose administration to healthy adult males.
(2) To investigate safety and tolerability of S-888711 in single-dose administration.

*: Hereinafter referred to as "S-888711 solution" in the tables and study results in this report.

Methodology:

S-888711 was administered to healthy adult male subjects as a single oral dose of 2 mg (crossover group) or 10 mg (10 mg group) to compare the incidences of adverse events (AEs) and adverse drug reactions (ADRs) and pharmacokinetic parameters (PK parameters) among the treatment groups.

In the crossover group, a set of procedures from admission through follow-up examination was repeated three times, and the 12-day washout periods were established. The post examination was performed on Day 13 of the third period for subjects in the crossover group and on Day 16 for subjects in the 10 mg group.

Crossover group

Cohort	First period		Second period		Third period	
	Hospitalization (5 days)	Post-discharge (8 days)	Hospitalization* (5 days)	Post-discharge (8 days)	Hospitalization* (5 days)	Outpatient visit after discharge (9 days)
1	Solution/fasted	Follow-up exam.	Tablet/fasted	Follow-up exam.	Tablet/fed	Follow-up exam. Post-exam.
2	Tablet/fed		Solution/fasted		Tablet/fasted	
3	Tablet/fasted		Tablet/fed		Solution/fasted	

* Examination on admission day at the second and third period will double as post-examination at the first and second period, respectively.

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:**	

10 mg group

Screening examination will be separately conducted for the crossover groups.

Hospitalization (5 days) Tablet/fed	Discharge (12 days)
	Follow-up examination Post-examination

Study Schedule

- Crossover group:

	Screening	(The following procedure will be repeated at the first to third period)								(The third period only)
		Hospitalization period (for 4 nights and 5 days)						Follow-up examination		Post-exam.
		Admission[b)] (the day before administration)	Day 1 (Before administration)	Day 1 (After administration)	Day 2	Day 3	Day 4	Day 6	Day 7	Day 13
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
Immunological tests	X									
Drug abuse screening urine tests	X	X								
Vital signs	X	X	X	X	X	X	X		X	X
Hematology tests[a)]	X	X	X		X	X	X		X	X
Blood biochemistry tests	X	X	X		X	X	X		X	X
Urinalysis	X	X	X		X	X	X		X	X
Platelet aggregation	X									
ECG	X	X	X	X	X	X	X		X	X
Blood sampling for measurement of plasma drug concentration			X	X	X	X	X	X	X	

a) Prothrombin time (PT) and activated partial thromboplastin time (APTT) will be measured at screening, 2 hours before and 4 hours after administration on Day 1, and on Day 4 only. Measurement at 4 hours after administration will include PT and APTT only.

b) Examination on admission day at the second and third period will double as post-examination at the first and second period, respectively.

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:**	

- 10 mg group:

	Screening	Hospitalization period (for 4 nights and 5 days)						Follow-up examination				Post-exam.
		Admission (the day before administration)	Day 1 (Before administration)	Day 1 (After administration)	Day 2	Day 3	Day 4	Day 6	Day 7	Day 10	Day 13	Day 16
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
Immunological tests	X											
Drug abuse screening urine tests	X	X										
Vital signs	X	X	X	X	X	X	X		X			X
Hematology tests[a)]	X	X	X		X	X	X		X	X	X	X
Blood biochemistry tests	X	X	X		X	X	X		X	X	X	X
Urinalysis	X	X	X		X	X	X		X	X	X	X
Platelet aggregation	X											
ECG	X	X	X	X	X	X	X		X			X
Blood sampling for measurement of plasma drug concentration			X	X	X	X	X	X	X		X	

a) Prothrombin time (PT) and activated partial thromboplastin time (APTT) will be measured at screening, 2 hours before and 4 hours after administration on Day 1, and on Day 4 only. Measurement at 4 hours after administration will include PT and APTT only.

Number of Subjects:

Target number of subjects: 26 (crossover group, 6 subjects/cohort × 3 cohorts; 10 mg group, 8 subjects)

Number of subjects randomized: 26 (crossover group, 6 subjects/cohort × 3 cohorts; 10 mg group, 8 subjects)

Number of subjects administered: 26 (crossover group, 6 subjects/cohort × 3 cohorts; 10 mg group, 8 subjects)

Number of subjects in the pharmacokinetic analysis set: 26

Number of subjects in the safety analysis set: 26

Diagnosis and Main Criteria for Inclusion

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.

Name of Sponsor: Shionogi & Co., Ltd.	**Individual Study Table Referring to Part of the Dossier Volume:**	(For National Authority Use Only)
Name of Finished Product: Not determined		
Name of Active Ingredient: S-888711	**Page:**	

(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 use of prescription or non-prescription drugs, including Chinese herbal medicine, dietary supplements, and vitamins etc, within 3 days prior to screening.
(2) The subject who has a history of regular use of tobacco or nicotine-containing products within 24 weeks prior to screening.
(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.
(4) The subject who has a history of use of platelet aggregation inhibitor 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 [chlorpromazine], prostaglandins [eg, prostandin], antibiotics [penicillin], anticoagulants [eg, heparin], antiplatelet drugs [eg, 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.
(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 and requires 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 to 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 disorder 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 appendectomy.
(15) The subject who has donated 400 mL of blood within 12 weeks or excess of 200 mL

Name of Sponsor: Shionogi & Co., Ltd.	**Individual Study Table Referring to Part of the Dossier Volume:**	(For National Authority Use Only)
Name of Finished Product: Not determined		
Name of Active Ingredient: S-888711	**Page:**	

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 cannot comply with items listed in "7. Control of Subjects" in the protocol.
(19) The subject who has positive test results for serologic test for syphilis (lipid antigen, TP antigen), hepatitis B surface antigen, hepatitis C virus antibody or human immunodeficient virus antibody.
(20) The subject who has received S-888711 before.
(21) The subject who is judged as an 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 or S-888711-containing solution formulation

2. Dosage and Administration

Crossover group: S-888711 2 mg solution product or 2 mg tablet
10 mg group: S-888711 10 mg tablet

3. Mode of Administration

(1) Crossover group

6 subjects per cohort × 3 cohorts (see the table below). Single-dose administration of the study drug to each cohort will be conducted at each period using the formulations (tablet or solution product) and administration conditions (fasted or fed condition) described below.

S-888711 2 mg tablet was orally administered with 240 mL of water for injection under fasted condition or after breakfast (fed condition) in the morning. Approximately 20 mL of S-888711 solution product prepared immediately before use will be administered once in the morning under fasted conditions with 20 mL of diluent solution for preparation of S-888711 solution and 200 mL (100 mL×2) of water for injection.

Cohort	First period	Second period	Third period
1	Solution/fasted (A)	Tablet/fasted (C)	Tablet/fed (B)
2	Tablet/fed (B)	Solution/fasted (A)	Tablet/fasted (C)
3	Tablet/fasted (C)	Tablet/fed (B)	Solution/fasted (A)

(2) 10 mg group

S-888711 10 mg tablet will be orally single-dose administered to 8 subjects after breakfast (fed condition) in the morning with 240 mL of water for injection.

4. Lot Number (Manufacturing Number)

Name of Sponsor: Shionogi & Co., Ltd. **Name of Finished Product:** Not determined **Name of Active Ingredient:** S-888711	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	(For National Authority Use Only)
S-888711 bulk drug, [redacted]; S-888711 2 mg tablet, [redacted]; S-888711 10 mg tablet, [redacted]		
Control Drug, Dose and Mode of Administration, Lot Number: No control drug was used in this study.		
Duration of Administration: One day (a total of 3 days in the crossover group, since administration was performed 3 times)		
Criteria for Evaluation: **1. Pharmacokinetic Evaluation** Based on measured plasma S-888711 concentrations, the following PK parameters were calculated and evaluated for each mode of administration and for each subject: maximum plasma concentration (Cmax), time to reach Cmax (Tmax), 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). **2. Safety Evaluation** The following safety variables were used for evaluation. (1) Subjective symptoms and objective findings (2) AEs (3) Presence or absence of abnormal change from baseline in laboratory test values (hematology and blood biochemical 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)		
Statistical Methods: **1. Pharmacokinetics Analysis** Based on measured plasma concentrations of S-888711, the PK parameters were calculated for each mode of administration in the crossover and 10 mg groups and for each subject. For each parameter, the arithmetic mean and its standard deviation (SD) and coefficient of variation (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 drug concentration-time curves, the results of pharmacokinetic analysis, etc. were plotted if required. Using log-transformed value for each PK parameter obtained in the crossover group, analysis of variance (ANOVA) was performed using cohort effect, period effect, treatment effect, and subject effect. Regarding comparison between the formulations (tablet/fasted vs. solution/fasted) and between the presence and absence of food effect (tablet/fed vs. tablet/fasted), the point estimate and its 90% confidence interval for the ratio of mean values of each PK parameter were calculated by ANOVA. For Tmax, ANOVA was performed without logarithmic transformation. **2. Safety Analysis**		

Name of Sponsor: Shionogi & Co., Ltd.	**Individual Study Table Referring to Part of the Dossier Volume:**	(For National Authority Use Only)
Name of Finished Product: Not determined		
Name of Active Ingredient: S-888711	**Page:**	

(1) Adverse events and adverse drug reactions

The numbers of subjects with any AE and ADR and the numbers of AEs and ADRs were tabulated for each mode of administration in the crossover and 10 mg groups, and the incidences of AEs and ADRs (i.e., percentages of subjects with AE and ADR among all evaluable subjects) and their 95% confidence intervals were calculated by the Clopper-Pearson method. The numbers of subjects with any AE and ADR and the numbers of AEs and ADRs in each treatment group were also counted according to the System Organ Class and Preferred Term. The frequency of data in each category regarding date of onset, severity, measures taken other than treatment with the study drug, seriousness, outcome, and causal relationship with the study drug were also analyzed.

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

For each mode of administration in the crossover and 10 mg groups, the descriptive statistics (N, mean, SD, minimum, median, and maximum) for each laboratory parameter at each time point were calculated. For qualitative test parameters, the frequency of data in each category at each time point was counted in a 2×2 contingency table. The frequencies of abnormal values and abnormal changes were also counted.

Summary - Conclusions

Pharmacokinetic Results:

PK parameters in the crossover and 10 mg groups

Treatment group	N	Cmax[a] (μg/mL)	Tmax[b] (hr)	AUC_{last}[a] (μg·hr/mL)	AUC_{inf}[a] (μg·hr/mL)	$t_{1/2,z}$[a] (hr)	CL/F[a] (L/hr)	MRT_{inf}[a] (hr)
2 mg solution/fasted	18	0.105 (14.2)	4.0 (3.0-10.0)	2.63 (23.5)	2.70 (22.9)	23.7 (17.5)	0.742 (22.9)	30.1 (14.6)
2 mg tablet/fasted	18	0.0932 (13.5)	4.0 (4.0-10.0)	2.45 (21.6)	2.51 (20.6)	23.4 (15.2)	0.797 (20.6)	30.6 (14.1)
2 mg tablet/fed	18	0.0842 (10.7)	5.0 (4.0-10.0)	2.25 (20.8)	2.31 (20.0)	23.2 (15.0)	0.866 (20.0)	31.2 (13.6)
10 mg tablet/fed	8	0.326 (17.1)	5.0 (4.0-10.0)	9.46 (19.6)	9.61 (20.0)	24.1 (11.3)	1.04 (20.0)	33.3 (9.3)

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

(Source: Pharmacokinetic Study Report Table 3a to 3d and Table 8)

The ratios of geometric mean Cmax, AUC_{last}, and AUC_{inf} values of 2 mg tablet to 2 mg solution in the fasted state were 0.890, 0.929, and 0.931, respectively, indicating that these values in tablet form were slightly lower than those in solution form. The $t_{1/2,z}$, and MRT_{inf} values in tablet form were similar to those in solution form, suggesting no significant difference in pharmacokinetics between the 2 formulations.

The ratios of geometric mean Cmax, AUC_{last}, and AUC_{inf} values of 2 mg tablet form in the fed state to that in the fasted state were 0.904, 0.921, and 0.920, respectively, indicating that absorption of S-888711 in the fed state was slightly lower than that in the fasted state. The Tmax, $t_{1/2,z}$, and MRT_{inf} values in the fed state were similar to those in the fasted state, suggesting no significant difference in pharmacokinetics between dietary conditions.

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		

The ratios of geometric mean Cmax, AUC_{last}, and AUC_{inf} values of the 10 mg tablet to the 2 mg tablet in the fed state were 3.87, 4.20, and 4.16, respectively, indicating that these values of the 10 mg tablet were higher than those of the 2 mg tablet in the fed state; the ratio of these parameters was slightly less than the dose ratio (5-fold).

Safety Results:

Five AEs were reported in 3 of 18 subjects in the crossover group. Two AEs in 1 subject in the solution/fasted cohort, 1 AE in 1 subject in the tablet/fasted cohort, and 2 AEs in 1 subject in the tablet/fed cohort were reported. Of these events, 4 AEs were handled to be ADRs in 2 of 18 subjects. Two ADRs were in 1 subject in the solution/fasted cohort and 2 ADRs were in 1 subject in the tablet/fed cohort.

AEs in the crossover group were as follows: 1 event each of WBC increased and neutrophil percentage increased in the solution/fasted cohort, 1 event of skin laceration in the tablet/fasted cohort, and 1 event each of WBC increased and neutrophil percentage increased in the tablet/fed cohort. No significant differences were found in the frequency or type of AEs between the different dosage forms (in 2 mg solution or 2 mg tablet) or between the presence and absence of meal at the time of administration of the tablet.

Three AEs were reported in 2 of 8 subjects in the 10 mg group. All AEs were handled to be ADRs. One event each of WBC increased, CRP increased, and urobilin urine present were reported.

No deaths, SAEs, or AEs leading to discontinuation occurred in all treatment groups. No abnormal ECG findings or abnormal changes in vital sign were found.

Although the skin laceration in the crossover group was judged as moderate in severity since it required treatment, all other AEs were abnormal changes in laboratory values without symptoms and signs; they were judged as mild in severity since they resolved without treatment. Since all AEs were confirmed to have resolved during the study period, it was confirmed that S-888711 was safe and well-tolerated under any of the dosing methods/conditions.

Conclusions:

Overall, the pharmacokinetics, safety and tolerability after a single oral dose of 2 mg in solution or tablet formulation in the fed or fasted state in a crossover study, and after a single oral dose of 10 mg in tablet form in the fed state were confirmed as follows:

- The difference in the pharmacokinetics between S-888711 2 mg tablet and 2 mg solution was slight, suggesting the 2 mg tablet provides comparable plasma exposure as the S-888711 solution.

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:**	

- The effect of food on the pharmacokinetics of S-888711 at 2 mg tablet was slight.
- There were no significant differences in safety and tolerability between the 2 formulations or between dietary conditions at a single dose of 2 mg S-888711.
- S-888711 was safe and well-tolerated at a single dose of 2 mg or 10 mg in tablet form.

Date of the Report: August 6, 2008

Date of the Amendment 1: 16 Nov 2017