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: To be determined	**Volume:**	
Name of Active Ingredient: S-888711	**Page:**	
Title of Study: A phase 1, randomized, double-blind, placebo- and positive-controlled, 4-period crossover, thorough QT/QTc study of S-888711 in healthy subjects		
Investigators: [redacted]		
Study Centers: [redacted]		
Publication: None		
Study Period: Six months between January [redacted], 2014 (date of the first administration of the study drug to the first subject) and June [redacted], 2014 (date of the final observation for the last subject)		
Phase of Development: 1		

Study Objectives:

Primary Objective:

- To compare the effect of single doses of 6 mg (exposure is equal to multiple dose of 3 mg, a therapeutic dose) and 24 mg (supratherapeutic dose) of S-888711 on the electrocardiogram (ECG) QT interval corrected for heart rate by Fridericia's correction (QTcF) with placebo

Secondary Objectives:

- To compare the effect of single doses of 6 mg and 24 mg of S-888711 on other ECG parameters (heart rate, PR, QRS, RR, QT, and ECG QT interval corrected for heart rate by Bazett's correction [QTcB]) with placebo
- To confirm the assay sensitivity by the assessment of the effect of moxifloxacin on the QTcF
- To assess the safety of single doses of 6 mg and 24 mg of S-888711 in healthy subjects
- To assess the pharmacokinetic (PK) profiles of single dose of 6 mg and 24 mg of S-888711 in healthy subjects
- To assess the correlation between S-888711 plasma concentration and the QTcF

Methodology:

This was a double-blind (in regard to S-888711), randomized, single-center, placebo- and positive-controlled, 4-period crossover study in 60 healthy subjects.

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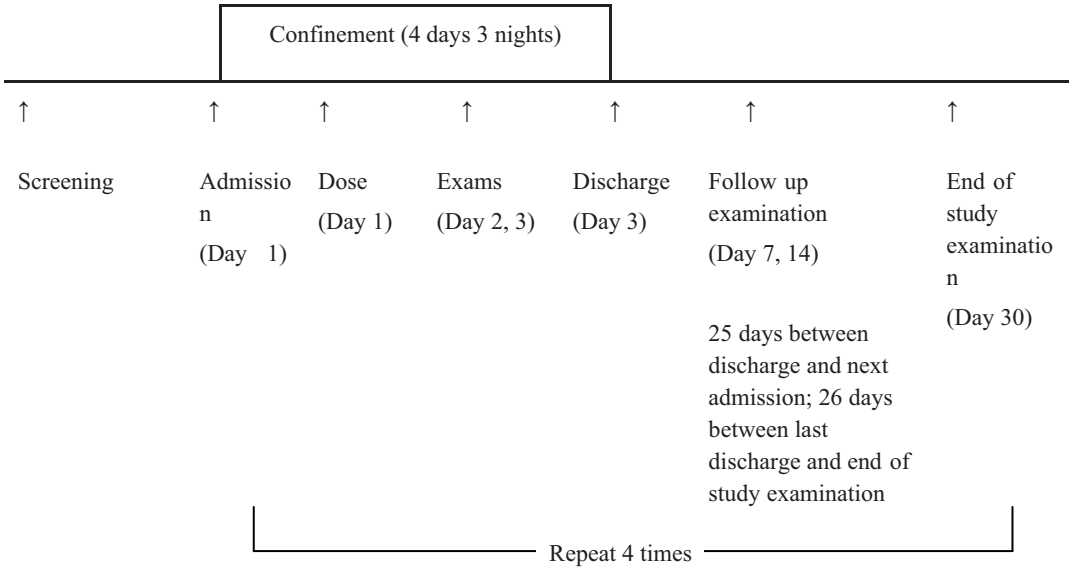
The study consisted of up to 28-day screening period, 117-day crossover period [29 days for each period plus 1 day], and 1 day end-of-study examination. After obtaining the informed consent, the eligible subjects were randomized to one of 4 treatment sequences (15 subjects per sequence) and received single doses of 6 mg of S-888711, 24 mg of S-888711, placebo for S-888711, or 400 mg of moxifloxacin on Day 1 of each period in the fasted state.

The randomized subjects completed 4 crossover periods (duration of Day 1 to the follow-up examination). The wash-out period was 28 days. The end-of-study examination was performed on Day 30 in the fourth period. The predose examinations on Day 1 in the second, third, and fourth period were performed as the examinations on Day 30 in the first, second, third period, respectively.



Number of Subjects:

Planned target sample size: 60 subjects

Randomized and administered subjects: 60 subjects

Analysis populations were as follows:

- QTc analysis population: 60 subjects
- Pharmacokinetic concentration population: 60 subjects
- PK parameter population: 59 subjects

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- PK/pharmacodynamics (PD) analysis population: 58 subjects
- Safety analysis population: 60 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 and female subjects aged between ≥ 20 and < 50 years at the time of signing the informed consent form.
3. Subjects whose body weight was ≥ 50 kg and body mass index (BMI) was between ≥ 18.5 and < 25.0.
4. Subjects who agreed to the following birth control requirements:

   Male subjects who were sterile or who agreed to use an appropriate method of contraception, including use of a condom with spermicide, from the admission day (Day 1) in the first period until 3 months after the last dose of study drug.

   Female subjects who agreed to use barrier contraception (including condom, diaphragm, and cervical cap) with spermicide or to use a highly-effective contraception (including contraceptive implant, injectable contraceptive, combination oral contraceptive, intrauterine contraceptive device, and vasectomized partner) from the admission day (Day 1) in the first period until 3 months after the last dose of study drug except for female subjects who were postmenopausal (defined as cessation of regular menstrual periods for 2 years or more and confirmed by a follicle-stimulating hormone test) or who were surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of such surgery.
5. Subjects who were considered as healthy by the investigator or subinvestigator at screening.
6. Subjects with platelet count within the reference range and platelet count of 300,000/μL or less at screening.

Exclusion Criteria:

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

1. Female subjects who had a positive pregnancy test at screening or the admission day (Day 1) in the first period.
2. Female subjects who were lactating.

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3. Subjects who had a history of cardiac disease or a history of prolongation of QT interval.
4. Subjects who had a family history of long QT syndrome.
5. Subjects who had a history of electrolyte abnormalities.
6. Subjects who had chronic disease requiring medication and/or other treatment such as dietary restriction and physical therapy.
7. Subjects who had any of the past or exsinting following diseases and were considered ineligible for this study by the investigator or subinvestigator: metabolic, hepatic, renal, hematological, respiratory, cardiovascular, gastrointestinal, endocrine, neurological, or psychiatric disease or other clinically-significant disease.
8. Subjects who had a family history of thrombosis, coagulation disorder, or thrombocytosis.
9. Subjects who had a history of operation, such as excision of stomach, vagal nerve and gut (except for appendectomy).
10. Subjects who had a hemorrhagic tendency.
11. Subjects who had a systolic blood pressure of ≤100 mmHg or ≥140 mmHg or a diastolic blood pressure of ≤ 60 mmHg or ≥ 90 mmHg at screening.
12. Subjects whose QTcF was more than 450 msec or heart rate (HR) was beyond the range of 50 to 95 bpm by 12-lead ECG after 10 minutes rest in a supine position at screening or on the admission day (Day 1) in the first period.
13. Subjects who had any abnormal finding on 12-lead ECG and were considered ineligible by the investigator or subinvestigator at screening or on the admission day (Day 1) in the first period.
14. Subjects who used any drugs (eg, prescription drugs, over-the-counter drugs, Chinese herbal, supplements, vitamins) within 3 days prior to screening.
15. Subjects who used tobacco or nicotine-containing smoking-cessation aid within 24 weeks prior to screening.
16. Subjects who had received cytochrome-P450 inhibitors (eg, itraconazole) or inducers (eg, rifampicin) within 4 weeks prior to screening.
17. Subjects who had a history of use of the following drugs within 4 weeks prior to screening:
    - drugs which decrease platelet aggregation ability including nonsteroidal anti-inflammatory drugs (eg, aspirin), coronary artery vasodilators (eg,

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dipyridamole), Ca-antagonists (eg, nifedipine), β-blockers (eg, atenolol), diuretics (eg, furosemide), psychotropic drugs (eg, chlorpromazine), prostaglandins, antibiotics (eg, penicillin), anticoagulants (eg, heparin), and antiplatelet drugs (eg, ticlopidine).

- thrombocytopenia-inducing drugs (eg, quinidine, valproic acid).
- hematinic drugs (eg, epoetin alfa).
- drugs or supplements that enhance the ability of platelet to aggregate (eg, vitamin K).

18. 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.
19. Subjects who had a history of hypersensitivity or serious side effects induced by a drug.
20. Subjects who had a history of allergic symptoms including food allergy but excluding inactive hay fever.
21. Subjects who had a history of abuse of alcohol or drugs.
22. Subjects who were positive urine screen for drug abuse at screening.
23. Subjects who were positive for any of the following tests at screening: syphilis (cardiolipin antibody, treponema-pallidum antibody), hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus antigen/antibody.
24. Subjects who could not conform to the items listed in "6. RESTRICTIONS" in the study protocol.
25. Subjects who had been exposed to other investigational drugs within 16 weeks prior to the initial dose in the first period.
26. Subjects who had received S-888711 or TPO agonists previously.
27. 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 3-mg tablet

Dose:

- S-888711 6-mg group: Two S-888711 3-mg tablets and 6 placebo tablets matching with S-888711 3-mg tablet.

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- S-888711 24-mg group: Eight S-888711 3-mg tablets.

Method of Administration:

An oral single dose in the fasted state.

Lot Number (Manufacturing Number):

S-888711 3-mg tablet, [redacted]

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

Control Drug (placebo tablets matching with S-888711):

Placebo tablets matching with S-888711 3-mg tablet

Dose:

- S-888711 placebo group: Eight placebo tablets matching with S-888711 3-mg tablet.

Method of Administration:

An oral single dose in the fasted state.

Lot Number (Manufacturing Number):

Placebo tablets matching with S-888711 3-mg tablet, [redacted]

Control Drug, Dose and Mode of Administration:

Control Drug (moxifloxacin):

Moxifloxacin 400-mg tablet prescribed at the study site

Dose:

- Moxifloxacin group: One moxifloxacin 400-mg tablet.

Method of Administration:

An oral single dose in the fasted state.

Duration of Administration: A single dose (1 day) in each of 4 periods.

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Criteria for Evaluation:

1. Continuous electrocardiogram (ECG) assessment

   a. QTc

   - The difference in QTcF change from baseline between the S-888711 group and the placebo group at each time point.
   - The difference in QTcB change from baseline between the S-888711 group and the placebo group at each time point.
   - QTcF change from baseline and QTcF at each time point.
   - QTcB change from baseline and QTcB at each time point.

   b. Other parameters, T-wave abnormality, the incidence of U-wave, and others.

2. PK assessment

Plasma concentrations and PK parameters, including maximum plasma drug concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration after dosing ($AUC_{0\ last}$).

3. Safety assessment:

- Adverse events (AEs) and adverse drug reactions (ADRs).
- Vital signs, clinical laboratory tests, safety ECG.

AEs were collected from the time of informed consent through the end-of-study/early termination examination. The investigator or subinvestigator performed the physical examination, clinical laboratory tests (hematology, blood chemistry, and urinalysis), vital sign measurement, and ECG measurement, and then confirmed any AEs. AEs reported after the initial dose of study drug or moxifloxacin were considered treatment-emergent AEs (TEAEs). The relationship of an AE to the study drug was categorized as not related, possibly related, probably related, or definitely related. ADRs are defined as any drug-related TEAE of which relationship is considered as possibly-, probably- or definitely-related.

Statistical Methods:

1. Continuous ECG analyses

   a. QTc data analyses

   ΔQTcF (defined as change form baseline) was analyzed by using a linear mixed-effects model with treatment, period, time point, period-by-time point interaction, and treatment-by-time point interaction as fixed effect terms, baseline as a covariate, and subject as a random effect. For this analysis, a two-sided 90%

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confidence interval was calculated for ΔΔQTcF (defined as placebo-subtracted change from baseline) for each treatment group at each time point. The primary analysis was whether the upper limits of 90% confidence interval of ΔΔQTcF do not exceed 10 msec to evaluate the effect of S-888711 on the ECG QT interval. The same analysis was performed for ΔQTcB.

The following categorical outliers were summarized:

- ΔQTcF of > 30 msec
- ΔQTcF of > 60 msec
- absolute QTcF values > 450 msec
- absolute QTcF values > 480 msec
- absolute QTcF values > 500 msec

b. Other parameters analyses

Descriptive statistics for heart rate, PR, QRS, RR, and QT interval and the changes from baseline for these parameters were presented. ECG findings were categorized at each time point. T-wave abnormality and the incidence of U-wave were summarized.

2. PK analyses

Plasma S-888711 and moxifloxacin concentrations were summarized by treatment and nominal sampling time. Time course profiles for plasma concentrations were presented graphically. The PK parameters of S-888711 were calculated for each treatment and subject based on the plasma S-888711 concentration data by the non-compartmental methods. The relationship between plasma S-888711 concentrations and ΔΔQTcF was evaluated.

3. Safety analyses

a. The incidences of AEs and ADRs

AEs were classified by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0. Of reported AEs in the case report form (CRF), TEAEs were used for safety analyses. The number of subjects experiencing TEAEs and the number of TEAEs were summarized by treatment group to calculate the incidence and its 95% confidence interval. The incidence was defined as the percentage of subjects experiencing TEAEs in the analysis population, and the confidence interval of the incidence was calculated based on the Clopper-Pearson method. TEAEs that led to death, serious TEAEs, significant TEAEs, TEAEs that led to withdrawal of study drug, ADRs, serious ADRs, significant ADRs, and ADRs that led to withdrawal of study drug were

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tabulated in a similar fashion.

For the summary of TEAE by system organ class and preferred term, the number of subjects who had experienced AEs was presented for each treatment group with the percentage of subjects. The summary of TEAEs was presented for severity by system organ class and preferred term.

All AEs including AEs that had presented prior to the first dose of the S-888711 or moxifloxacin were listed.

b. Clinical laboratory tests, vital signs, and safety ECG,

Descriptive statistics and the changes from baseline were presented at each time point. Qualitative laboratory test data were classified according to test category at each time point. Safety ECG findings were categorized at each time point.

Summary - Conclusions

PK and PD Results:

The least squares (LS) means of ΔΔQTcF were ≤ 3 msec and their upper limits of 90% confidence interval were ≤ 10 msec at any time point for the 6-mg and 24-mg doses of S-888711. This result complied with the definition of negative thorough QT/QTc study in the ICH guideline. No difference was found between the S-888711 6- and 24-mg groups. In contrast, significant QT/QTc prolongation was found for moxifloxacin because the LS mean of ΔΔQTcF was > 5 msec and the lower limit of 90% confidence interval exceeded 0 msec at any time point. Thus, it was considered that the study had assay sensitivity. These results indicated that single doses of 6 and 24 mg of S-888711 did not influence QT interval.

No subjects with ΔQTcF > 30 msec were reported. The number of subjects with QTcF > 450 msec was 1 of 57 subjects (1.8%) in the S-888711 24-mg group and 4 of 57 (7.0%) in the moxifloxacin group, but no subjects had QTcF > 480 msec.

No significant relationship was found between ΔΔQTcF and plasma S-888711 concentration. The slope of plasma S-888711 concentration versus ΔΔQTcF relationship in the PK/PD model was not statistically significant, and the upper limits of 90% confidence interval for predicted mean ΔΔQTcF at C_{max} for 6 mg and 24 mg were ≤ 10 msec.

Safety Results:

- A total of 43 TEAEs occurred in 23 of 60 subjects (38.3%): 13 TEAEs in 9 of 59 subjects (15.3%) in the S-888711 6-mg group, 14 TEAEs in 12 of 57 subjects (21.1%) in the S-888711 24-mg group, 9 TEAEs in 8 of 57 subjects

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(14.0%) in the moxifloxacin group, and 7 TEAEs in 5 of 59 subjects (8.5%) in the placebo group.

- A total of 12 ADRs occurred in 11 of 60 subjects (18.3%): 2 ADRs in 2 of 59 subjects (3.4%) in the S-888711 6-mg group, 8 ADRs in 8 of 57 subjects (14.0%) in the S-888711 24-mg group, 1 ADR in 1 of 57 subjects (1.8%) in the moxifloxacin group, and 1 ADR in 1 of 59 subjects (1.7%) in the placebo group.
- All the TEAEs were mild or moderate, and all the ADRs were mild. No deaths, serious adverse events (SAEs), severe AEs, or AEs leading to discontinuation occurred.
- TEAEs occurring in at least 2 subjects in any of the S-888711 groups were as follows: platelet count increased (8 subjects in the 24-mg group), γ-glutamyltransferase increased (2 subjects in the 6-mg group and 1 subject in the 24-mg group), blood bilirubin increased (2 subjects in the 6-mg group, 2 subjects in the 24-mg group, 1 subject in the moxifloxacin group, and 2 subjects in the placebo group), upper respiratory tract inflammation (3 subjects in the 6-mg group and 1 subject in the moxifloxacin group). All the events except the platelet count increased occurring in 8 subjects in the 24-mg group were considered not related to the study drug.
- Among the laboratory tests, platelet count increased, γ-glutamyltransferase increased, and blood bilirubin increased were considered TEAEs, but the changes were not clinically significant.
- No clinically significant changes were found in vital signs or ECG.

Conclusions:

- Single doses of 6 and 24 mg of S-888711 did not influence QT interval in healthy subjects.
- Single doses of 6 and 24 mg of S-888711 were safe and well-tolerated in healthy subjects.

Date of the Report: 29 October 2014

Date of the Amendment 1: 16 Nov 2017