SYNOPSIS

Sponsor: **Shionogi USA, Inc.**	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: **S-888711**	**Volume:**	
Name of Active Ingredient: **TBD**	**Page:**	

Study Title:

A Phase I Multiple-dose, Double-blind Placebo-controlled Study to Assess the Safety and Pharmacokinetics of S-888711 in Healthy Subjects

Investigator and Study Center:

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Publication (reference): see Appendix 12.1.11

Studied Period:

█ February 2009 (first subject enrolled) to
█ June 2009 (last subject completed)

Study Phase: 1

Objectives:

The objective of this study was to determine the safety, tolerability, and pharmacokinetics (PK) of multiple oral doses of S-888711 in healthy adult subjects.

Methodology: This was a 14-day randomized, double-blind, placebo-controlled, ascending multiple-dose study with subjects enrolled to 1 of the 4 following dosing cohorts:

- Cohort A: 0.25 mg/day (1 x 0.25 mg tablet) of S-888711 or matching placebo
- Cohort B: 0.5 mg/day (2 x 0.25 mg tablets) of S-888711 or matching placebo
- Cohort C: 0.75 mg/day (3 x 0.25 mg tablets) of S-888711 or matching placebo
- Cohort D: 1.0 mg/day (4 x 0.25 mg tablets) of S-888711 or matching placebo

The study consisted of screening (Days -28 to -3), admission to the clinical research unit (CRU; Day -2), confirmation of enrollment eligibility status (Day -1), administration of study drug or matching placebo (Days 1 to 14), follow-up safety assessments (Days 15 to 28), and a final end-of-study visit (EOS), which occurred 7 ± 2 days after the date of discharge (Day 35 ± 2).

Prospective subjects were screened beginning at 4 weeks prior to the date of the planned first dosing of the study drug. Subjects who met the inclusion criteria and did not meet any exclusion criteria were enrolled into the study. A total of 32 subjects were enrolled with

8 subjects assigned to 1 of the 4 cohorts. Each of the 8 subjects within a particular cohort was randomly assigned to 1 of the 2 treatment groups based on the next available allocation from the randomization schedule. Six subjects were randomly assigned to the active S-888711 group and 2 subjects were randomly assigned to the placebo group.

Subjects who were enrolled in the study were admitted to the CRU 2 days before study drug administration and remained in the CRU for the 14-day drug administration and the 14-day follow-up periods. Subjects were continuously monitored for safety during their entire 30-day CRU admission. Each subject was discharged from the CRU after all Day 28 safety assessments were completed and were to return to the CRU 7 ± 2 days later for a final end of-study visit (Day 35 ± 2).

Cohorts A and B were conducted in parallel, with Cohort A starting 7 days before Cohort B. After the completion of these 2 cohorts, the sponsor, investigator, and medical monitor reviewed the safety data. Following an acceptable safety evaluation of the data, Cohorts C and D were then conducted sequentially. A second safety evaluation of the data was conducted following the completion of Cohort C, prior to dosing Cohort D.

During the entire course of each dosing cohort, the results of each subject's platelet count were compared to that subject's baseline (Day 1 predose) value.

Treatment for an individual subject was stopped if that subject's platelet count was >1.5 x the baseline platelet value.

Dose escalation to the next cohort did not occur if:

- One or more subjects in any cohort developed severe adverse events (AEs), irrespective of AE relationship   to study drug.
- Two or more subjects in any cohort developed moderate AEs, irrespective of AE relationship to study drug.
- Five or more subjects in any cohort had a platelet count of >1.5 x the baseline platelet value.

Number of Subjects (Planned and Analyzed):

Thirty-two subjects were planned; 32 subjects were analyzed for safety; 32 subjects were included in the analyses of PK variables.

Diagnosis and Main Criteria for Inclusion:

Healthy males or females of nonchildbearing potential, 18 to 55 years of age who had body mass index (BMI) of $\geq$ 18.5 to $\leq$ 32 kg/m^2, a body weight $\geq$ 50 kg, a platelet count of 100,000 to 325,000/µL, and had platelet aggregation test results of $\geq$ 55% of platelet maximum aggregation rate induced by adenosine diphosphate (ADP) or collagen at screening.

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

S-888711 (0.25 mg) tablet, oral, lot number ███████

Duration of Treatment: 14 days

Reference Therapy, Dose and Mode of Administration, Lot Number:

Placebo indistinguishable from S-888711 0.25 mg tablet but containing no active S-888711, oral, lot number █████

Criteria for Evaluation:

Safety:

Safety evaluation assessed AEs, treatment-emergent AEs, vital signs (blood pressure, pulse, respiratory rate, body temperature), ECG findings (heart rate, QT interval, RR interval, QT corrected by Fridericia's formula [QTcF]), laboratory tests (hematological tests, prothrombin time [PT], activated partial thromboplastin time [APTT], International Normalized Ratio [INR], biochemical tests (including thyroid-stimulating hormone [TSH], thyroxine [T4], and serum cortisol), and urinalysis), platelet aggregation (maximum aggregation with ADP and collagen), and any other parameters that were relevant for safety assessment.

Pharmacokinetics

The following PK parameters were determined for S-888711 and where possible for its major metabolites (S-888711 deshexyl and S-888711 5-keto).

C_{max}	Maximum observed plasma concentration for Days 1, 7, and 14
t_{max}	The time that C_{max} was observed for Days 1, 7, and 14
AUC_{0-24hr}	Area under the concentration-time curve from time zero to time 24 hours. Calculated by linear trapezoidal rule for Days 1, 7, and 14.
AUC_{0-last}	Area under the concentration-time curve from time zero to the last quantifiable concentration; calculated using linear trapezoidal rule for Days 1, 7, and 14
AUC_{0-inf}	Area under the concentration-time curve from time zero to infinity for Days 1, 7, and 14. Calculated as $AUC_{0-last} + C_{last}/\lambda_z$
$t_{\frac{1}{2},}$	Terminal elimination half-life; calculated as $0.693/\lambda_z$, for Days 1, 7, and 14.
λ_z	The terminal elimination rate constant based on data points in the terminal phase for Days 1, 7, and 14.
CL/F	Apparent total clearance. Calculated through the formula dose/AUC from the S-888711 AUC and dose. Calculated for the Days 1, 7, and 24. AUC is either AUC_{0-inf} after a single dose (Day 1) or AUC_{0-24hr} for Days 7 and 14.
R_{Cmax}	C_{max} accumulation ratio during multiple dosing for Days 7 and 14. Calculated by dividing the C_{max} of the Day 7 and Day 14 dosing by the C_{max} of the initial dosing
R_{AUC}	AUC accumulation ratio during multiple dosing for Days 7 and 14. Calculated by dividing the $AUC_{0-24\ hr}$ of the Day 7 and Day 14 dosing by the AUC_{0-24hr} of the initial dosing.
Ur (%)	Urinary excretion ratio on each day from Day 1 to Day 14. Calculated through the formula Ur (%) = Ae/dose × 100, where Ae is the urinary excretion amount calculated from the urinary concentration and urine volume.
Ur,total (%)	Cumulative urinary excretion ratio to final measurement of cumulative dose from Day 1 to Day 19. Calculated through the formula Ur, total (%) = total Ae/total dose × 100, where total Ae is the cumulative urinary excretion amount from Day 1 to Day 19 and total dose is the cumulative daily dose from Day 1 to Day 14.

$R_{M/D,AUC}$ Ratio of AUC of metabolites to AUC of unchanged S-888711. Calculated from the AUC_{0-inf} for the initial dosing and the AUC_{0-24hr} for the Day 7 and Day 14 dosing.

Statistical Methods:

Analysis Populations

The All Randomized set of subjects included all subjects enrolled into the study. Unless otherwise stated, data listings used the set of All Randomized subjects.

The Safety Population was defined as all subjects who received at least 1 dose of study drug.

Safety data were analyzed and summarized for the Safety Population.

The PK Full Analysis Population included all subjects who received at least 1 dose of study drug and had at least 1 PK sample analyzed.

Pharmacokinetic data were listed for the PK Full Analysis Population.

The PK Evaluable Population included all subjects who received at least 1 dose of study drug and had sufficient PK samples evaluated for calculation of PK parameters at least on Day 1.

Pharmacokinetic data were analyzed and summarized for the PK Evaluable Population.

Analysis Plan

Unless otherwise noted, continuous variables were summarized using number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables were summarized using the frequency count and the percentage of subjects in each category.

No imputation was applied for missing data. Only non-missing values were used for analyses.

All subject data collected during this study including data not appearing in tables, were presented in data listings.

Unless otherwise noted, all listings were sorted by treatment group, subject number, and study day.

Safety:

Adverse events were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 12). The incidence and frequency (number of subjects) of treatment-emergent AEs, and the number of reported treatment-emergent AEs were summarized by treatment group. The denominator for incidence was the total number of subjects within each treatment group in the safety population.

Treatment-emergent AEs, SAEs, severe AEs, AEs related to study medication (defined as possibly, probably, or definitely related to study drug), and AEs that lead to study discontinuation were summarized in a similar manner to treatment-emergent AEs.

Continuous laboratory parameters were summarized descriptively by treatment group for each time point collected and for the change from baseline (Day 1 predose) to each time point.

The measurements of each subject were plotted against time by treatment group.

For qualitative data, the frequency counts and percentages of the qualitative results were

presented for each timepoint where data were collected.

Quantitative clinical laboratory test data were classified as low, normal, or high, and qualitative clinical laboratory test data were classified as normal or abnormal, based on prespecified normal or reference ranges. Shift tables of the change relative to the normal ranges from baseline (Day 1 predose) to end of treatment were presented.

A listing of out-of-range laboratory values for relevant laboratory parameters was provided.

In addition to calculation of change from baseline (Day 1 predose), percentage change from baseline in platelet count was summarized descriptively by treatment group for each time point.

Also, mean (standard deviation) profile plot was presented by treatment group for each of the following: platelet count, change from baseline in platelet count, and percentage change from baseline in platelet count.

Vital signs were summarized descriptively by treatment group for each time point measured and for the change from baseline (Day 1 predose) to each time point.

The measurements of each subject were plotted against time by treatment group.

Physical examination changes from baseline (Day 1 predose) to each timepoint were summarized in shift tables.

Summary statistics for ECG findings were presented by treatment group for each timepoint measured and for the change from baseline to each timepoint. The mean of 3 measurements observed within 2 hours before dosing was summarized descriptively, and was used as the baseline value.

The measurements of each subject were plotted against time by treatment group. The mean of measurements observed within 2 hours before dosing was used as observation at Day 1 predose in these graphs.

Pharmacokinetics

Actual elapsed time relative to the start of dosing was used for all parameter estimations. If λ_z could not be determined, $t_{1/2}$ and AUC_{0-inf} were not estimated for that study day. If the calculated R^2 value for λ_z was less than 0.8 then that subject's $t_{1/2}$ and AUC_{0-inf} were flagged in the data listing, but not excluded from the analysis. In addition to the parameters listed above, the ratio of $100*(AUC_{0-inf} - AUC_{0-last})/AUC_{0-inf}$ were determined for each subject. If the ratio was greater than 20% then that subjects AUC_{0-inf} was flagged in the data listing, but not excluded from the analysis.

Plasma and urine concentration-time data for S-888711 and its major metabolites (S-888711 deshexyl and S-888711 5-keto) were presented in descriptive summary tables, individual listings, mean profile plots, and individual profile plots.

Urinary excretion amount data for S-888711 and its major metabolites (S-888711 deshexyl and S-888711 5-keto) were presented in descriptive summary tables and individual listings.

Descriptive summaries of plasma concentration, urine concentration and excretion amount data included number of observations (n), the arithmetic mean value and its standard deviation and coefficient of variation (% CV), and the geometric mean value and its coefficient of variation (% geoCV), median, minimum, and maximum.

Descriptive summaries of PK parameters included n, the arithmetic mean value and its standard deviation and % CV, and the geometric mean value and its % geoCV, median, minimum and maximum. The t_{max} parameter was presented only as n, median, minimum, and maximum. Pharmacokinetic parameters at Days 1, 7, and 14, and Ur (%) were also presented in mean profile plots and individual profile plots.

C_{max}, AUC_{0-24hr} and AUC_{0-inf} of S-888711, S-888711 deshexyl and S-888711 5-keto were assessed for dose proportionality by day (Days 1, 7, and 14) using the power model. The power model assumed a linear relationship between the natural log-transformed (ln-transformed) parameter and the ln-transformed dose.

In the case where dose proportionality was not established over the entire dosing range, the ratios of C_{max}, AUC_{0-24hr} and AUC_{0-inf} were examined between dose groups on each day.

The relationships between dose and C_{max}, AUC_{0-24hr}, or AUC_{0-inf} at Days 1, 7, and 14 were graphically presented.

Dose independence of PK parameters of S-888711 was examined between the dose groups on Days 1, 7, and 14. For $t_{1/2}$, CL/F, and Ur (%) of S-888711, S-888711 deshexyl and S-88711 5-keto, the ratios between dose groups were examined for dose independence using the an analysis of variance (ANOVA) model on Days 1, 7, and 14. The point estimates and 90% CIs were generated for the differences of all dose group combinations for ln-transformed $t_{1/2}$, CL/F and Ur (%). The point estimates and 90% CIs for the differences between each dose group combination were back-transformed to obtain the corresponding geometric mean ratios and their 90% CIs.

The differences of C_{max} and AUC_{0-24hr} of S-888711, S-888711 deshexyl and S-888711 5-keto between Days 1, 7, and 14 in each dose group were assessed for the accumulation ratios of C_{max} and AUC_{0-24hr} (Day 7/Day 1 and Day 14/Day 1) and for the evaluation of steady state (Day 14/Day 7). Analysis of variance was performed and 90% CIs were generated for the differences between Days 1, 7, and 14 for ln-transformed C_{max} and AUC_{0-24hr} in each dose group, separately. The corresponding 90% CIs for the geometric mean ratios were obtained by taking the antilog of the 90% CIs for the differences between each day combination.

Time independence of PK parameters of S-888711, S-888711 deshexyl and S-888711 5-keto was examined between Days 1, 7, and 14 in each dose group. The differences of AUC (AUC_{0-inf} on Day 1 and AUC_{0-24hr} on Days 7 and 14), $t_{1/2}$, CL/F, and Ur (%) between all day combinations in each dose group were assessed. Analysis of variance was performed and 90% CIs were generated for the differences between all day combinations for ln-transformed AUC, $t_{1/2}$, CL/F, and Ur (%) in each dose group.

Summary of Results

Pharmacokinetic:

The mean concentration time profile of S-888711 increased in a dose-dependent manner. For all 4 dose groups, Days 7 and 14 demonstrated higher drug exposure compared to Day 1.

There were only a few quantifiable plasma concentrations of S-888711 deshexyl following administration of 0.25 mg S-888711. The mean concentration time profile of S-888711

deshexyl was higher following administration of 1.0 mg S-888711 compared to 0.5 mg and 0.75 mg administration. For S-888711 5-keto, there was no quantifiable plasma concentration in 0.5 mg and 0.75 mg dose groups, only 2 measurable concentrations in 0.25 mg dose group, and a few quantifiable concentrations in 1.0 mg dose group. For both S-888711 deshexyl and 5-keto, the 1.0 mg dose group exhibited higher drug exposure than other dose groups.

C_{max} and AUC (AUC_{0-24}, AUC_{0-last}, and AUC_{0-inf}) demonstrated a dose-dependent increase on each of Days 1, 7, and 14. For each dose group, C_{max} and AUC were higher on Days 7 and 14 compared to Day 1.

S-888711 was slowly absorbed and eliminated. For all 4 dose groups, C_{max} was reached within 5 hours after dosing, with individual T_{max} values ranging from 5 to 36 hours trending longer at higher dose levels. The mean ($\pm$ SD) terminal $t_{1/2}$ of S-888711 on Day 14 was 29.4 ± 1.77 hours, 28.5 ± 3.03, 27.1 ± 3.28, and 27.7 ±4.34 hours following the administration of 0.25, 0.5, 0.75, and 1.0 mg of S-888711, respectively. The mean (± SD) oral CL/F on Day 14 following the administration of 0.25, 0.5, 0.75 and 1.0 mg of S-888711 was 1.34 ± 0.262, 1.46 ± 0.266, 1.45 ± 0.325, and 1.30 ± 0.028 L/h, respectively.

The C_{max}, AUC_{0-24}, and AUC_{0-inf} of S-888711 on Days 1, 7, and 14 were assessed for dose proportionality using a power model. For all parameters assessed and on all 3 study days, the value of estimated slope was close to 1 and the 95% confidence interval (CI) contained 1 (within the range of 0.733 to 1.228), indicating dose proportionality over the studied dose range.

Effects of dose on $t_{1/2}$ and CL/F of S-888711 were examined on Days 1, 7, and 14 using an ANOVA model. The CL/F and $t_{1/2}$ were similar across all dose groups. The geometric mean ratios for CL/F ranged from 88.85% (1.0 mg versus 0.5 mg on Day 7) to 109.20% (0.5 mg versus 0.25 mg on Day 14) and the geometric mean ratios for $t_{1/2}$ ranged from 98.13% (0.75 mg versus 0.25 mg on Day 7) to 102.14% (1.0 mg versus 0.75 on Day 7). For each pairwise comparison of dose, the 90% CI contained 100%, indicating dose-independence of S-888711 $t_{1/2}$ and CL/F over the studied dose range.

The C_{max} and AUC_{0-24} values on Day 7 were similar to those on Day 14. For C_{max}, the geometric mean ratios (%) for Days 14 to 7 values were 94.32, 100.91, 97.34, and 100.74 for the 0.25. 0.5, 0.75, and 1.0 mg dose groups, respectively. For AUC_{0-24}, the geometric mean ratios (%) from Days 14 to 7 values were 97.72, 96.53, 94.58, and 97.28 for the 0.25, 0.5, 0.75, and 1.0 mg dose groups, respectively. For each comparison of Day 14 to Day 7, the 90% CI contained 100%, indicating achievement of steady state by Day 7.

The AUC_{0-24} and CL/F values on Day 7 were similar to those on Day 14. For AUC_{0-24}, the geometric mean ratios were 97.72, 96.20, 94.21, and 92.36 for the 0.25, 0.5, 0.75, and 1.0 mg dose groups respectively. For CL/F, the geometric mean ratios were 102.44, 103.96, 106.09, and 108.41 for the 0.25, 0.5, 0.75, and 1.0 mg dose groups respectively. For all comparisons, the 90% CI contained 100%, indicating time-independent PK over the studied time range.

Safety:

A total of 32 subjects were enrolled into the study. All 32 subjects were included in the Safety Population and all 24 subjects who received S-888711 were included in the PK Full Population and the PK Evaluable Population. All 32 enrolled subjects were listed as completing the study. Seven subjects had study drug discontinued as they met the individual stopping rule. This result was not unexpected given the known biological action of S-888711.

All 7 subjects completed the protocol-defined safety assessments and were therefore included in the Safety Population. No clinically important trends were identified between treatment groups in regards to demographics, medical history, or prior and concomitant medication use. No treatment compliance issues with study drug administration were identified and no clinically important protocol deviations were reported.

Overall, 19 subjects experienced treatment-emergent AEs. None of the treatment-emergent AEs were reported as severe or serious. Three subjects (2 from the pooled placebo group and 1 from the 1.0 mg dose group) reported treatment-emergent AEs that were considered related to study drug. No subject was withdrawn from the study due to a treatment-emergent AE. Headache, dizziness, and fatigue were most common treatment-emergent AEs reported, with the highest incidence of headache and dizziness reported in the 0.75 mg dose group. There were no apparent dose-response relationships identified regarding the types or incidences of treatment-emergent AEs reported during the study.

A dose-response relationship was observed between platelet count increase and the dose of S-888711. Hematocrit and hemoglobin decreased during the study in all treatment groups, including placebo with no apparent dose response relationship. These decreases are consistent with the volume of blood drawn in this study. Median and mean serum cortisol level exhibited a greater drop from baseline to Day 35/EOS in the 0.75 mg and 1.0 mg dose groups compared to other groups. However, this shift must be interpreted with caution given the individual subject variability in response, the large SD, small sample size, and limited sampling days (baseline and Days 14 and 35 [EOS]). Several abnormal dermatological findings at EOS were reported without any safety trend or concerns identified. Several of these abnormal dermatological finding appeared to be related to skin irritation from the ECG electrodes. No apparent clinically relevant trends regarding blood chemistry, coagulation, urinalysis, physical examinations, thyroid function, vital signs, or ECG assessments were identified.

CONCLUSIONS

Pharmacokinetic Conclusions:

- C_{max} and AUC increase in a dose dependent manner
- C_{max} and AUC_{0-24} are dose proportional at Days 1, 7, and 14
- Steady state was achieved by Day 7
- $t_{1/2}$ and CL/F are independent of dose
- CL/F is independent of time
- The PK of S-888711 is linear over the studied dose range

Safety Conclusions:

- S-888711 was well tolerated at the 4 dosing regimes evaluated
- No safety or tolerability concerns were identified in this study

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