

## SYNOPSIS

**Sponsor:** Shionogi USA, Inc. **Individual Study Table** **(For National Authority Use only)**

**Referring to Part of the Dossier**

**Name of Finished Product:** **Volume:**

TBD

**Name of Active Ingredient:** **Page:**

S-888711

### Study Title:

An Open-label, Randomized, Three-period, Crossover Study to Assess the Effect of Food and Calcium on S-888711 0.25-mg Tablet Pharmacokinetics in Healthy, Adult Volunteer Subjects Following a Single 0.75-mg Oral Dose of S-888711

### Investigator and Study Center:

[REDACTED]

**Publication (reference):** see [Appendix 12.1.11](#)

### Study Period:

[REDACTED] November 2009 (first subject screened) to  
[REDACTED] December 2009 (last subject completed)

**Study Phase:** Phase 1

### Objectives:

The primary objectives of this study were:

- To assess the effect of a high-fat diet on the pharmacokinetics (PK) of a 0.75-mg single dose of S-888711 orally administered as 0.25-mg tablets in healthy volunteer subjects
- To assess the effect of a calcium supplement on the PK of a 0.75-mg single dose of S-888711 orally administered as 0.25-mg tablets in healthy volunteer subjects

The secondary objective of this study was:

- To assess the safety of a 0.75-mg single dose of S-888711 orally administered as 0.25-mg tablets in healthy volunteer subjects

**Methodology:** This was a Phase 1, open-label, single-dose, randomized, 3-period crossover study to evaluate the effect of food and calcium on the PK of S-888711 in healthy subjects. Fifteen male and female subjects in good general health were selected to participate in this study. The study consisted of Screening (Days -14 through -7), 3 study periods (confinement: Days -1 through 3; Days 11 through 14; and Days 22 through 25; and outpatient: Days 4 and 5, Days 15 and 16, and Days 26 and 27), and a final End-of-Study Visit (Days 35 to 40) performed 10 to 15 days following discharge from Study Period 3 confinement. All study periods were separated by a 5-day washout period. Dosing occurred on the second day of confinement in each study period (Days 1, 12, and 23). Prospective

subjects were screened beginning 7 to 14 days prior to the first planned dose of S-888711. Subjects who met the inclusion criteria and did not meet any exclusion criteria were randomized on Day -1 of Study Period 1 to 1 of 3 regimen sequences. Subjects received all 3 regimens in a crossover fashion according to their randomized regimen sequence. For each study period, confinement to the clinical research unit (CRU) began in the evening prior to dosing (Days -1, 11, and 22) and continued for a minimum of 48 hours after dosing (Days 3, 14, and 25). On Day 1 of each study period, subjects received a single 0.75-mg dose of S-888711 orally at approximately 8:00 AM. Subjects were dosed under fasting or fed conditions, with or without calcium carbonate, in each study period as determined by the regimen sequence to which they were randomized. Subjects who received Regimen A fasted 10 hours prior to dosing with S-888711 orally and remained fasting until 4 hours after dosing, when lunch was provided. Subjects who received Regimen B fasted 10 hours prior to receiving a standardized high-fat/high-calorie/low-calcium breakfast 30 minutes prior to dosing with S-888711 orally, which was consumed within 30 minutes, and no food was allowed for at least 4 hours after dosing, when lunch was provided. Subjects who received Regimen C took 4000 mg of calcium carbonate with their S-888711 oral dose; these subjects fasted 10 hours prior to dosing and remained fasting until 4 hours after dosing, when lunch was provided. Across all regimens, meals were standardized throughout the confinement, with the exception of breakfast on Day 1 during which Regimens A and C fasted and Regimen B received a high-fat/high-calorie/low-calcium breakfast. S-888711 0.75 mg was orally administered with 240 mL of water. Water was allowed ad libitum during confinement except for 1 hour before or 2 hours after S-888711 dosing. During each study period, blood samples for PK analysis of plasma S-888711 concentrations were collected prior to dosing and over a 96-hour period following dosing (1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours after dosing).

**Number of Subjects (Planned and Analyzed):**

Fifteen subjects were planned; 15 subjects were analyzed for safety; 14 subjects were included in the analyses of PK variables.

**Diagnosis and Main Criteria for Inclusion:**

Healthy males or females of nonchildbearing potential  $\geq 18$  and  $\leq 70$  years of age, inclusive who had body mass index (BMI) of  $\geq 19$  to  $\leq 29.9$  kg/m<sup>2</sup>, and a platelet count of 100,000 to 325,000/ $\mu$ L.

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

S-888711 0.25-mg light red film-coated tablet for oral administration. All 3 regimen groups received 0.75 mg of S-888711 (3 tablets); lot number [REDACTED]

**Duration of Treatment:** S-888711 was administered once in each study period.

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

Not applicable.

**Criteria for Evaluation:**

**Safety:**

Safety was assessed by monitoring of clinical laboratory evaluations (including hematology, blood biochemistry, and urinalysis), vital signs, 12-lead electrocardiograms (ECGs), and physical examinations. Treatment-emergent adverse events (AEs) and serious AEs (SAEs)

were to be collected and tabulated.

### Pharmacokinetics:

The WinNonlin<sup>®</sup> computer program (WinNonlin Professional Network Edition, version 5.2, [REDACTED]), using a noncompartmental analysis method, was utilized to obtain the following PK parameters:

Parameter	Description
$C_{max}$	Maximum observed plasma concentration
$t_{max}$	Time to maximum observed plasma concentration
$AUC_{0-last}$	Area under the concentration-time curve from time zero to the time point of the last quantifiable concentration; calculated using the trapezoidal rule
$AUC_{0-inf}$	Area under the concentration-time curve from time zero to infinity; calculated as $AUC_{0-last} + C_{last}/\lambda_z$
$t_{1/2,z}$	Terminal elimination half-life; calculated as $\ln 2/\lambda_z$
$\lambda_z$	Terminal elimination rate constant based on data points in the terminal phase
CL/F	Apparent total clearance; calculated as $dose/AUC_{0-inf}$ (S-888711 only)

### Statistical Methods:

#### Analysis Populations

**Enrolled Subjects:** A subject was considered as “enrolled” if eligibility requirements were met and the subject was assigned a subject number at Day 1 of Study Period 1. Unless otherwise stated, data listings presented data for all enrolled subjects.

**Safety Population:** The Safety Population was defined as all subjects who received at least 1 dose of study drug, including a partial dose. Safety data were analyzed and summarized for the Safety Population.

**Pharmacokinetic Full Analysis 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. Concentration data were listed and summarized for the PK Full Analysis Population. Pharmacokinetic parameters were calculated and listed for the PK Full Analysis Population.

**Pharmacokinetic Evaluable 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 at least 1 PK parameter for each treatment period. Pharmacokinetic parameters were analyzed and summarized for the PK Evaluable Population.

#### Subject Accountability

The following data were summarized; all percentages were based upon the number of subjects enrolled: number of subjects enrolled, number (%) of subjects who completed the study, number (%) of subjects who discontinued early and reason for early discontinuation, and number (%) of subjects in the Safety, PK Full Analysis and PK Evaluable Populations.

### Subject Demographics

Summary statistics were presented for demographics and subject characteristics at Screening, for the Safety Population, for PK Full Analysis Population and for the PK Evaluable Population.

### Concomitant Medications

Prior and concomitant medications were coded using the World Health Organization Drug Dictionary (Sep2009 standard) to preferred terms. All reported concomitant medications were presented in data listings. The listings included all data collected as well as the preferred term.

### Pharmacokinetic Data:

Plasma concentration time data for S-888711 and where possible for 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. Descriptive summaries of plasma concentration included number of observations (n), the arithmetic mean value and its standard deviation and coefficient of variation (% CV), the geometric mean value and its coefficient of variation (% geoCV), median, minimum, and maximum. Plasma PK parameter data for S-888711 and where possible for its major metabolites (S-888711 deshexyl and S-888711 5-keto), were presented in descriptive summary tables and in data listings.

Descriptive summaries of PK parameters included n, the arithmetic mean value and its standard deviation and % CV, the geometric mean value and its % geoCV, median, minimum, and maximum. The  $t_{\max}$  parameter was summarized only with n, median, minimum, and maximum. Analyses of variance were performed on the natural logarithms of  $C_{\max}$ ,  $AUC_{0-\text{last}}$ ,  $AUC_{0-\text{inf}}$ ,  $\lambda_z$ ,  $t_{1/2,z}$ , and CL/F of S-888711, with fixed effects for sequence, period, and regimen, and a random effect for subject nested within sequence.

The relative bioavailability of S-888711 from Regimens B and C to that from Regimen A was assessed from  $C_{\max}$ ,  $AUC_{0-\text{last}}$ , and  $AUC_{0-\text{inf}}$ . The ratio of geometric means and the corresponding 90% confidence intervals (CIs) were estimated by exponentiating the least squares mean difference and CI in the logarithm. If the 90% CI was completely contained within the range of 80% to 125%, then the conclusion held that the 2 regimens were equivalent.

### Safety:

Adverse events were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>; version 12). The incidence and frequency of treatment emergent AEs (TEAEs), SAEs, severe AEs, AEs related to study drug (defined as possibly related, or related to study drug), and AEs that led to study discontinuation were to be presented for each regimen. For each of the frequency tables, all TEAEs were tabulated. A separate listing of deaths, other SAEs, and other significant AEs was provided.

Continuous laboratory parameters for hematology, blood biochemistry and urinalysis were summarized descriptively for each scheduled time point collected (1 day predose, dosing day: 2 hours predose, 1 day postdose, and 2 days postdose) and for the change from baseline to each time point, by regimen. 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 reference ranges. Shift tables of the change relative to the normal ranges from baseline to 2 days postdose were presented by regimen. A listing of

abnormal laboratory values for relevant laboratory parameters was provided.

Vital signs were summarized descriptively for each scheduled time point collected (1 day predose, morning predose, 2 hours postdose, 1 day postdose, and 2 days postdose) and for the change from baseline (morning predose) to each time point, by regimen. For the overall Safety Population, the change from Screening to the End-of-Study and from Screening to Early Termination was presented. Shifts from Screening to Days -1, 11, and 22 and at End-of-Study in physical examination findings were presented by regimen. Symptom focused physical examination findings observed at 2 days postdose were reported by regimen. Summary statistics for ECG findings were presented for Screening, End-of-Study/Early Termination and the change from Screening to the End-of-Study/Early Termination for the overall Safety Population.

## Summary of Results

### Pharmacokinetic:

The mean S-888711 plasma concentration-time profiles following the administration of Regimens A, B and C were similar, and demonstrated slow absorption and elimination phases of the study drug. After attaining peak concentration, there were some suggestions that the decline of S-888711 plasma concentrations may follow a biphasic pattern.

S-888711 was first quantifiable at 1 hour postdose, with the exception of Subject [REDACTED]. For this subject, predose concentrations were detected in Study Period 2 (Regimen B; 0.106 ng/mL) and Study Period 3 (Regimen C; 0.108 ng/mL). Both concentrations were just above the assay quantification limit and were <1% of the  $C_{max}$  values of the subject (17.7 ng/mL and 19.7 ng/mL for Regimen B and C, respectively), and consequently, both values were included in the PK parameter calculations.

Intersubject variability for the S-888711 PK parameters  $C_{max}$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf}$ ,  $t_{1/2,z}$ , and  $CL/F$  was low to modest (geometric % CV ranged from 7.9% to 30.2%), and comparable between the 3 regimens.

The median  $t_{max}$  was slightly longer, with a slightly wider range of individual values for Regimen B, when S-888711 was administered in the fed state.

The geometric means for  $C_{max}$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf}$ , and  $CL/F$  of S-888711 were similar between the 3 regimens, with Regimen B exhibiting the lowest intersubject variability, as evidenced by the geometric % CV.

Terminal elimination half-life appeared to be the same in the 3 regimens, and similar between individual subjects within each regimen as evidenced by the low geometric % CV values (7.9% to 15.6%).

For each of assessed parameters  $C_{max}$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf}$ ,  $\lambda_z$ ,  $t_{1/2,z}$ , and  $CL/F$ , the geometric mean ratios for Regimen B to A comparison and Regimen C to A comparison were both close to 100%. The corresponding 90% CIs for both comparisons for all 6 parameters were within the predefined equivalence criteria of 80% to 125%.

### Safety:

Of the 15 subjects who were included in the Safety Population, 4 (26.7%) subjects experienced at least 1 TEAE during the study. One subject experienced a TEAE during both Regimens A and C. These 4 subjects reported a total of 7 TEAEs. The TEAEs reported during Regimen C included headache (2), nausea (2), diarrhea (1), and contact dermatitis (1).

The only other TEAE reported by any subject was in Regimen A, which had a single report of constipation. Subjects [REDACTED] and [REDACTED] reported headaches during Regimen C that were considered as moderate. All other TEAEs reported during the study were considered mild. None of the TEAEs were reported as possibly related or related to study drug, ie, all were considered not related. All of the subjects recovered from all TEAEs and no action was taken in regard to the study drug. There were no SAEs, deaths, or discontinuations due to an AE. No clinically relevant trends regarding blood chemistry, hematology, urinalysis, physical examinations, vital signs, or ECG assessments were identified.

## **CONCLUSIONS**

### **Pharmacokinetic Conclusion:**

Neither a high-fat diet nor coadministration with 4000 mg of calcium carbonate had a clinically meaningful effect on the PK of a 0.75-mg single dose of S-888711 orally administered as three 0.25-mg tablets in healthy volunteer subjects, suggesting the absence of a PK interaction with either food intake or polyvalent cations (eg, antacids, mineral supplements, and dairy products).

### **Safety Conclusion:**

The study drug was well tolerated and no safety issues were identified.

**Final Date:** 11 August 2010

**Prepared in:** Microsoft Word