SYNOPSIS

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

Study Title:

A Phase 1, Open-label, One-sequence Crossover, Drug-drug Interaction Study to Evaluate the Effect of Repeated Doses of S-888711 on the Pharmacokinetics of the CYP3A4 Substrate, Midazolam, in Healthy Subjects

Investigator and Study Center:

████████████████
███████████████████

Publication (reference): see Appendix 12.1.11

Studied Period:

█ August 2009 (first subject enrolled) to
█ September 2009 (last subject completed)

Study Phase: 1

Objectives: The primary objectives of this study were:

• to determine the effect of multiple-dose S-888711 administration on the pharmacokinetics (PK) of midazolam;

• to assess the safety of S-888711 during multiple-dose administration and when coadministered with midazolam.

Methodology: This was a Phase 1, open-label, one-sequence crossover study to evaluate the effect of repeated S-888711 doses on the PK of the cytochrome P450 3A4 (CYP3A4) substrate, midazolam, in healthy subjects. Fifteen subjects in good general health were selected to participate in this study. The study consisted of Screening (Days -14 through -3), admission to the clinical research unit (CRU; Day -2), confirmation of enrollment eligibility status (Day -1), administration of midazolam alone (Day 1), administration of S-888711 alone (Days 2 through 7), administration of midazolam and S-888711 (Day 8), follow-up safety assessments (Days 9 through 15), and a final End-of-Study Visit (Day 22 ± 2), which occurred 7 ± 2 days after the date of discharge.

Prospective subjects were screened beginning 14 days prior to the first planned midazolam administration. Subjects who met the inclusion criteria and did not meet any exclusion criteria were enrolled into the study. Enrolled subjects were admitted to the CRU 2 days prior to the first dose of midazolam and remained in the CRU for the 8-day dosing period and the 7-day follow-up period. Subjects were monitored continuously for safety during their 17-day CRU admission. Each subject was discharged from the CRU after all Day 15 safety

assessments were completed and returned to the CRU within 7 ± 2 days for a final End-of-Study Visit (Day 22 ± 2).

A 5-mg dose of midazolam was administered on Day 1; PK samples were obtained prior to dosing and over the next 24 hours following dosing. S-888711 was administered on Days 2 through 7, starting with a 1.5-mg dose on Day 2, followed by a 0.75-mg dose on Days 3 through 7. Pharmacokinetic samples were obtained prior to dosing on Days 2 through 7 to confirm trough S-888711 levels. On Day 8, a 5-mg dose of midazolam and a 0.75-mg dose of S-888711 were coadministered; PK samples for both drugs (and metabolites) were obtained prior to dosing and over the next 24 hours following dosing.

Number of Subjects (Planned and Analyzed):

Fifteen subjects were planned; 15 subjects were analyzed for safety; 15 subjects were included in the analyses of PK variables. (PK Full Analysis Set, n=15 subjects; PK Evaluable Population, n=15 subjects)

Diagnosis and Main Criteria for Inclusion:

Healthy males and 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, and a platelet count of 100,000 to 325,000/μL.

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

S-888711 (0.25-mg) tablet for oral administration: light red film-coated tablet containing 0.25 mg of S-888711; lot number ▉▉▉▉▉ .

Duration of Treatment: 5 mg of Midazolam on Days 1 and 8; 1.5 mg of S-888711 on Day 2 and 0.75 mg on Days 3 through 8.

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

Midazolam (2 mg/mL) syrup for oral administration: clear, red to purplish-red, cherry-brandy flavored syrup containing midazolam hydrochloride equivalent to 2 mg/mL manufactured by Roche, lot number: ▉▉▉▉▉ .

Criteria for Evaluation:

Safety:

Safety evaluation assessed adverse events (AEs), treatment-emergent AEs, vital signs (blood pressure, heart rate, respiratory rate, body temperature), ECG findings (heart rate, QT interval, RR interval, QT corrected by Fridericia's formula), laboratory tests (hematological tests, prothrombin time, activated partial thromboplastin time, International Normalized Ratio, biochemistry tests, and urinalysis), platelet aggregation (maximum aggregation with ADP and collagen), and any other parameters that were relevant for safety assessment.

Pharmacokinetics:

The WinNonlin$^®$ computer program (WinNonlin Professional Network Edition, version 5.2, ▉▉▉▉▉▉▉▉▉▉▉▉▉▉), 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 for midazolam and α-hydroxymidazolam on Day 1 and Day 8
AUC_{0-inf}	Area under the concentration-time curve from time zero to infinity; calculated as $AUC_{0-last} + C_{last}/\lambda_z$ for midazolam and α-hydroxymidazolam on Day 1 and Day 8
$AUC_{0-\tau}$	Area under the concentration-time curve over the dosing interval τ (ie, 24 hours); calculated by the trapezoidal rule using actual elapsed time without extrapolation for S-888711 and its major metabolites on Day 8
$t_{1/2}$	Terminal elimination half-life; calculated as $0.693/\lambda_z$
λ_z	Terminal elimination rate constant based on data points in the terminal phase
CL/F	Apparent total clearance; calculated through the formulae $dose/AUC_{0-inf}$ for midazolam on Day 1 and Day 8 and $dose/AUC_{0-\tau}$ for S-888711 on Day 8.

Statistical Methods:

Subject Accountability

The following data were summarized: number of subjects enrolled, number (%) of subjects who completed the study, number (%) of subjects who discontinued early, and number (%) of subjects in each analysis population.

Subject Demographics

The following parameters were summarized: age, gender, race, ethnicity, height, weight, BMI, and presence or absence of medical history.

Concomitant Medications

Prior and concomitant medications were coded using the World Health Organization (WHO) Drug Dictionary (March 2009 standard) to preferred terms and reported in a data listing.

Pharmacokinetic Data

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

Plasma PK parameter data for midazolam, α-hydroxymidazolam, S-888711 and its major metabolites were presented in descriptive summary tables and in data listings.

An analysis of variance (ANOVA) considering treatment as fixed effect and subject as random effect was performed for the following parameters of midazolam and α-hydroxymidazolam: the natural logarithm of C_{max}, AUC_{0-last}, AUC_{0-inf}, λ_z, and CL/F.

The ratio of geometric means and the corresponding 90% confidence intervals (CIs) were estimated by exponentiating the least square (LS) mean difference and CI in the logarithm. For the primary parameters, midazolam C_{max}, AUC_{0-last}, and AUC_{0-inf}, if the 90% CI was completely contained within the range of 80 to 125%, then the conclusion was that repeated S-888711 doses did not affect the PK of midazolam.

Safety

Adverse events were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 12.

The incidence and frequency of treatment-emergent: AEs, SAEs, severe AEs, AEs related to study drug, and AEs that led to study discontinuation were presented for each study period (midazolam dosing period, S-888711 dosing period, midazolam and S-888711 coadministered dosing period, follow-up periods and overall).

The incidence and frequency of treatment-emergent AEs were summarized by system organ class and preferred term, by system organ class, preferred term and severity, and by system organ class, preferred term and relationship to study drug.

Continuous laboratory parameters (hematology, blood biochemistry, urinalysis, and platelet aggregation), vital signs, and ECG findings were summarized descriptively for each scheduled timepoint collected and for the change from baseline to each timepoint.

For laboratory parameters, shift tables of the change relative to the normal ranges from baseline to Day 9, from baseline to Day 22 were presented.

Physical examination changes from baseline to each timepoint were summarized in shift tables.

Summary of Results:

Pharmacokinetic

The mean midazolam plasma concentration-time profiles following single-dose administration of midazolam (Day 1) were similar to that following a single midazolam dose administered during daily S-888711 dosing at steady state (Day 8). Intersubject variability for the midazolam PK parameters C_{max}, AUC_{0-last}, AUC_{0-inf}, and CL/F was moderate (% geo CV ranged from 25.1% to 32.5%) and comparable between the 2 dosing periods. Higher intersubject variability of λ_z and $t_{1/2}$ was evident as larger % geoCV values (39.4% for Day 1 and 54.9% for Day 8) were estimated. The geometric means for midazolam C_{max}, AUC_{0-last}, and AUC_{0-inf} were similar following a single-dose administration of midazolam alone on Day 1 and following a single midazolam dose administered during daily S-888711 dosing at steady-state. Although the median midazolam T_{max} differed slightly between study days (0.5 hours and 0.75 hours on Day 1 and Day 8, respectively), the ranges of individual T_{max} values were the same (0.5 to 1.0 hours) on both study days. The geometric mean λ_z of midazolam was 0.165 on Day 1 and 0.186 on Day 8. The geometric mean of corresponding $t_{1/2}$ was 4.21 hours on Day 1 and 3.74 hours on Day 8.

The mean α-hydroxymidazolam plasma concentration-time profiles were similar following a single-dose administration of midazolam (Day 1) and following a single midazolam dose administered during daily S-888711 dosing at steady state (Day 8).

Intersubject variability for α-hydroxymidazolam parameters C_{max}, AUC_{0-last}, and AUC_{0-inf} was moderate (% geoCV ranged from 17.7% to 38.4%) and comparable between the 2 dosing periods. Higher intersubject variability for λ_z and $t_{1/2}$ was evident as larger % geoCV values (69.2% for Day 1 and 88.4% for Day 8) were estimated. The geometric mean value of C_{max} of α-hydroxymidazolam was similar following a single dose administration of midazolam alone on Day 1 and following a single midazolam dose administered during daily S-888711 dosing at steady state. The geometric mean values of AUC_{0-last} and AUC_{0-inf} were slightly higher on Day 8 compared to that on Day 1. The

AUC$_{0-inf}$ of α-hydroxymidazolam could only be determined for 5 and 7 subjects on Day 1 and Day 8, respectively. The median T$_{max}$ of midazolam was 0.5 hours and 0.75 hours on Day 1 and Day 8, respectively. However, the ranges of individual T$_{max}$ values were the same (0.5 to 1.0 hours) at both study days. The λ$_z$ of α-hydroxymidazolam could only be determined for 7 and 8 subjects on Day 1 and Day 8, respectively. The geometric mean value of λ$_z$ was 0.146 on Day 1 and 0.155 on Day 8. The geometric mean value of corresponding t$_{1/2}$ was 4.75 hours on Day 1 and 4.48 hours on Day 8.

Mean concentration-time profiles of S-888711 on Day 8 following multiple-dose administration of S-888711 showed slow absorption and elimination phases of the study drug. Peak concentration of S-888711 was observed about 4 hours postdose, which was followed by a rapid decline by 6 hours and a relatively slow terminal phase after 8 hours. The predose concentration-time profile of S-888711 indicated that steady-state of S-888711 was achieved by Day 5. Steady-state PK parameters of S-888711 and metabolite S-888711 deshexyl exhibited moderate intersubject variability, as evidenced by the % geoCV of geometric means (from 22.0% to 34.9%). The median T$_{max}$ (5 hours) and the range of individual T$_{max}$ values (0.5 to 12 hours) were the same for both S 888711 and S-888711 deshexyl. The λ$_z$ and the corresponding t$_{1/2}$ were either non-determinable or poorly estimated in all subjects for both S-888711 and metabolite S-888711 deshexyl.

For the primary parameters, the Day 8 to Day 1 geometric mean ratios (GMRs) for C$_{max}$ (101.26%), AUC$_{0-last}$ (103.84%), and AUC$_{0-inf}$ (103.58%) were all close to 1. The corresponding 90% CIs were all within the predefined equivalence criteria of 80% to 125%. For CL/F, the GMR was 96.54%, with 90% CI 90.15% to 103.38%. The Day 8 to Day 1 GMR of λ$_z$ of midazolam was 111.22%.

The Day 8 to Day 1 GMR of C$_{max}$ (102.71%) of α-hydroxymidazolam was close to 1. The corresponding 90% CI was within the 80% to 125% predefined equivalence criteria. The geometric mean AUC$_{0-last}$ of α-hydroxymidazolam increased by 15.8% from Day 1 to Day 8. The upper bound (127.74%) of 90% CI was just above the upper limit (125%) of predefined equivalence criteria. The geometric mean AUC$_{0-inf}$ increased by 23.4% from Day 1 to Day 8. The corresponding 90% CI (101.35% to 150.15%) was not contained within the predefined equivalence criteria of 80% to 125%. The Day 8 to Day 1 GMR of λ$_z$ was 110.67%.

Safety

All 15 enrolled subjects completed the protocol-defined administration of study drug and safety assessments. No safety-related issues were identified in regard 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, 8 subjects experienced 14 treatment-emergent AEs during the study. There was no significant difference in incidence or frequency of treatment-emergent AEs across the dosing periods. Sedation was the most commonly reported treatment-emergent AE, which was reported by 2 subjects (Subjects ██████ and ██████) during the midazolam alone dosing period and 1 subject (Subject ████) during both the S-888711 alone and midazolam plus S-888711 dosing periods. Other than sedation, no other treatment-emergent AE was reported more than once during any 1 dosing period and overall no other treatment-emergent AE was reported by more than 1 subject during the entire study. All of the treatment emergent AEs were assessed by the investigator as mild. Two subjects had the treatment-emergent AE of

sedation assessed as related to the study drug during the midazolam alone dosing period. All other treatment-emergent AEs were assessed as unlikely related or not related to the study drug.

Mean platelet count increased gradually and steadily from baseline ($236 \times 10^3/mm^3$) through Day 11, reaching plateau at Day 15 ($302 \times 10^3/mm^3$), and then gradually decreased toward baseline levels at Day 22 ($255 \times 10^3/mm^3$). No other clinically relevant trends regarding blood chemistry, hematology, urinalysis, physical examinations, or vital signs and ECG assessments were identified.

CONCLUSIONS

Pharmacokinetic Conclusion:

•   The presence of drug interaction effects on midazolam PK by multiple dose administration of S-888711 was rejected based on assessment of C_{max}, AUC_{0-last}, and AUC_{0-inf}, suggesting S-888711 is not an inhibitor or inducer of CYP3A.

Safety Conclusions:

•   No safety concerns were identified in this study.

•   Coadministration of S-888711 and midazolam was well tolerated.

Final Report Date: 09 February 2010

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