2. SYNOPSIS

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Study Title: A Phase 1, Open-label, Randomized, Three-period Crossover Drug-drug Interaction Study to Evaluate the Effect of Cyclosporine and/or Quinidine Sulfate on the Pharmacokinetics of S-888711 in Healthy Adult Subjects

Investigator and Clinical Research Unit:

[redacted]

Publication (Reference): None

Studied Period:

[redacted] July 2015 (first subject enrolled) to
[redacted] September 2015 (last subject completed)

Study Phase: 1

Objectives:

The primary objective of the study was:

To compare the pharmacokinetics (PK) of a single dose of S-888711 3 mg co-administered with cyclosporine 400 to 600 mg or quinidine sulfate (hereafter, quinidine) 600 mg to the PK of a single dose of S-888711 3 mg administered alone in healthy adult male subjects.

The secondary objective of the study was:

To assess the safety and tolerability of a single dose of S-888711 3 mg co-administered with cyclosporine 400 to 600 mg or quinidine 600 mg in healthy adult male subjects.

Methodology:

A single-center, open-label, randomized, 3-period crossover, drug-drug interaction (DDI) study to assess the effect of cyclosporine, a known inhibitor of permeability-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), or quinidine, a known inhibitor of P-gp, on the PK of S-888711 in healthy adult male subjects.

Eligible subjects were randomized to one of 2 treatment sequences and received S-888711 or S-888711 and cyclosporine in the first or second period as the table below. The subjects were to receive S-888711 and quinidine in the third period. The study protocol specified that whether the third period was to be conducted or not was judged by the magnitude of increase in C_{max} and AUC of S-888711 in the first and second periods but that if the upper limit of 90% confidence intervals (CIs) for the ratio

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of S-888711 maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of S-888711 co-administered with cyclosporine relative to S-888711 dose alone were 125% or less, the third period was not to be conducted. Actually, the third period was cancelled because the magnitude of increase in C_{max} and AUC of S-888711 in the first and second periods did not warrant the third period.

Treatment Sequence	First Period	Second Period	Third Period (Not Conducted)
1	S-888711	S-888711 + Cyclosporine	S-888711 + Quinidine
2	S-888711 + Cyclosporine	S-888711	S-888711 + Quinidine

Number of Subjects (Planned and Analyzed):

One subject randomized to the treatment sequence 2 was withdrawn from the study by the subject's request on Day 5 in the first period. The other 7 subjects randomized to the treatment sequence 2 were withdrawn from the study after the completion of the first period due to the inappropriate handling of blood samples for measurement of blood cyclosporine concentrations. In consideration of the withdrawals, additional 8 subjects were enrolled and assigned to the treatment sequence 2 in order to attain the primary objective.

Number of subjects planned: 16 (8 for each treatment sequence)

Number of subjects enrolled: 24 (8 for the treatment sequence 1, 16 for the treatment sequence 2)

Number of subjects who completed the study: 16 (8 for each treatment sequence)

Number of subjects analyzed for PK: 24 (8 for the treatment sequence 1, 16 for the treatment sequence 2)

Number of subjects analyzed for safety: 24 (8 for the treatment sequence 1, 16 for the treatment sequence 2)

Diagnosis and Main Criteria for Inclusion:

This study enrolled healthy male subjects aged ≥ 20 to < 50 years with body mass index (BMI) of ≥ 18.5 to < 30.0 and a body weight ≥ 50 to ≤ 85 kg.

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

Test Product: S-888711 3-mg tablet

Dose and Mode of Administration:

Each subject received a single dose of 3 mg of S-888711 (one S-888711 3-mg tablet) in

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the fasted state on Day 1 in each period.

Lot Number: [redacted]

Reference Therapy, Dose and Mode of Administration:

Test Product: Cyclosporine (Neoral® 50-mg capsules)

Dose and Mode of Administration:

Each subject received a single dose of 400 to 600 mg of cyclosporine (eight to twelve Neoral® 50-mg capsules) in the fasted state on Day 1 in the first or second period. The dose of cyclosporine was adjusted based on body weight; 400 mg for subjects weighing between ≥ 50 and < 65 kg, 500 mg for subjects weighing between ≥ 65 and < 75 kg, and 600 mg for subjects weighing between ≥ 75 and < 85 kg.

Lot Number: [redacted] and [redacted]

Duration of Treatment:

Two days: 2 single doses of S-888711 (1 day for each period) and 1 day of a single dose of cyclosporine.

Duration of Study Participation:

Study duration in individual subjects was up to 70 days (up to 28-day screening period, 42-day crossover period [21 days for each period])

Criteria for Evaluation:

Pharmacokinetic Analysis:

In each period, blood samples for PK analysis of plasma S-888711 concentrations were collected pre-dose, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, and 144 hours post-dose.

In the period during which cyclosporine was administered, blood samples to measure blood cyclosporine concentrations were collected pre-dose, and 1, 2, 4, 6, 12, and 24 hours post-dose.

Pharmacokinetic Parameters:

The following PK parameters were calculated based on the plasma S-888711 and the blood cyclosporine concentration data with the non-compartmental methods: C_{max}, time to maximum plasma/blood concentration (T_{max}), AUC from time zero to the time of the last quantifiable concentration after dosing ($AUC_{0\text{-last}}$), AUC extrapolated from time zero to infinity ($AUC_{0\text{-inf}}$), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2,z}$), apparent total clearance (CL/F), and apparent volume of distribution (V_z/F).

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Safety Assessment:

Safety was assessed by monitoring of physical examinations, vital signs, electrocardiogram (ECG), clinical laboratory tests (including hematology, blood chemistry, and urinalysis), treatment-emergent adverse events (TEAEs), treatment-related AEs, and serious adverse events (SAEs).

Statistical Methods:

Pharmacokinetics:

The PK parameters of S-888711 after co-administration of S-888711 with cyclosporine and after administration of S-888711 alone were compared using the analysis of variance (ANOVA) considering treatment, treatment sequence, and period as fixed effect; and subject as random effect for the following parameters of S-888711: the logarithm of C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, λ_z, $t_{1/2,z}$ and CL/F. The ratio of the geometric least squares means and the corresponding 90% CI were estimated by exponentiating the difference in the means and the corresponding 90% CI in the logarithm.

If the 90% CIs of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were completely contained within the range of 80.00% to 125.00%, the conclusion would be that inhibitor of P-gp and BCRP does not affect the PK of S-888711.

Safety:

Safety and tolerability data were summarized descriptively. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0. The number of subjects who experienced any TEAEs, treatment-related AEs, TEAEs that led to study discontinuation, significant TEAEs, or SAEs was counted, and the incidence and its 95% CI were summarized for each treatment group. The 95% CIs were calculated by using the Clopper-Pearson method. The number of subjects with TEAEs was tabulated by system organ class and preferred term. Summary statistics for vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), ECG evaluations (heart rate, QT, PR, and QTc-intervals), and laboratory test evaluations (hematology, blood chemistry, and urinalysis) were calculated.

Summary of Results

Pharmacokinetics:

The results of ANOVA for C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, λ_z, $t_{1/2,z}$ and CL/F of S-888711 to evaluate the effect of cyclosporine on the PK of S-888711 are shown below. Co-administration with cyclosporine increased S-888711 C_{max} by 18% and AUC ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) by 19% compared with S-888711 alone. The upper limit of 90% CI for C_{max} was less than 125.00%, and those for $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were

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slightly higher than 125.00% but closed to 125.00%. These results suggested the effect of co-administration with cyclosporine on the PK of S-888711 was slight.

Results of Statistical Analysis for the Effect of Cyclosporine on the PK of S-888711 (PK Parameter Population; N = 16)

	GLS Mean		Ratio	90% CI	
Parameter	**S-888711 Alone (A)**	**S-888711 + Cyclosporine (B)**	**(B/A)**	**Lower**	**Upper**
C_{max} (ng/mL)	111	131	1.1777	1.1147	1.2442
$AUC_{0\text{-last}}$ (ng·hr/mL)	2876	3426	1.1911	1.1314	1.2539
$AUC_{0\text{-inf}}$ (ng·hr/mL)	2931	3491	1.1910	1.1317	1.2534
λ_z (1/hr)	0.0259	0.0265	1.0223	0.9809	1.0653
$t_{1/2,z}$ (hr)	26.8	26.2	0.9782	0.9387	1.0194
CL/F (L/hr)	1.02	0.859	0.8396	0.7978	0.8836

Whether the third period would be conducted or not was to be determined based on the ratios of C_{max} and AUC of S-888711 co-administered with cyclosporine relative to S-888711 dose alone as follows: if the upper limits of 90% CIs for the ratios of C_{max} and AUC of S-888711 co-administered with cyclosporine relative to S-888711 dose alone are ≤125%, the third period will not be conducted. Consequently, as described above, the upper limit of 90% CI for C_{max} was less than 125.00%, and those for $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were slightly higher than 125.00% but closed to 125.00%. These results suggested that P-gp and BCRP inhibition had a slight effect on the PK of S-888711. The results, close to the pre-specified criteria, were considered such that an evaluation of an effect of quinidine on the PK of S-888711 was not required. Therefore, the third period was cancelled.

Safety:

A total of 12 TEAEs were reported in 8 of the 24 subjects (33.3%) in the period of co-administration of S-888711 with cyclosporine, and no TEAEs were reported in the period of administration of S-888711 alone. All the TEAEs were considered not related to S-888711 by the investigator or subinvestigator. Thus, there was no treatment-related AE. All the TEAEs were mild and resolved without any intervention during the study. The most frequent TEAE was feeling hot reported in 7 subjects (29.2%). No deaths, SAEs, or AEs leading to withdrawal from the study were reported. No clinically significant abnormal findings for clinical laboratory test results including platelet count, vital sign measurements, or ECGs were reported.

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CONCLUSIONS

Pharmacokinetics:

- Co-administration with cyclosporine increased S-888711 C_{max} by 18% and AUC by 19% compared with S-888711 alone, suggesting a slight effect of co-administration with cyclosporine on the PK of S-888711. Therefore, it could be concluded that P-gp and BCRP inhibition had a slight effect on the PK of S-888711.

Safety:

- A single 3 mg dose of S-888711 was safe and well-tolerated when administered alone or co-administered with cyclosporine to healthy adult subjects.

Final Report Date: 27 January 2016

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