2. SYNOPSIS

Sponsor: Shionogi, Inc.	**Individual Study Table:** Referring to Part of the Dossier	(For National Authority Use only)
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Study Title:

A Phase 1, Open-label, Randomized, 2-way Crossover Study to Evaluate the Drug-drug Interaction of the P-gp inhibitor Cyclosporine with the Pharmacokinetics of S-297995 in Healthy Adult Subjects

Investigator and Study Center:

[redacted]

Publication: None

Studied Period:

[redacted] February 2012 (first subject signed consent form) to
April 2012 (last subject completed)

Study Phase: Phase 1

Objectives:

The primary objective of the study was:

- To determine the effect of a single dose of cyclosporine on the pharmacokinetics (PK) of a single dose of S-297995 in healthy adult subjects.

The secondary objectives of the study were:

- To evaluate the safety of S-297995 when co-administered with cyclosporine.
- To evaluate the PK of S-297995, its metabolites (Nor-S-297995 and S-297995 3-O-β-D-glucuronide), and cyclosporine.

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Methodology:

This was a phase 1, open-label, 2-way crossover study. The PK and safety of S-297995 when co-administered with cyclosporine were explored. Fourteen healthy subjects were randomly assigned to 2 groups of 7 to 1 of 2 treatment sequences. The study design was as follows:

Sequence 1: Seven subjects received 0.4 mg of S-297995 orally (po) alone on Period 1 (Day 1) in the fasted state and S-297995 co-administered po with 600 mg of cyclosporine solution United States Pharmacopeia (USP) (modified) po on Period 2 (Day 15) in the fasted state.

Sequence 2: Seven subjects received 0.4 mg of S-297995 po co-administered with 600 mg of cyclosporine solution USP (modified) po on Period 1 (Day 1) in the fasted state and S-297995 alone on Period 2 (Day 15) in the fasted state.

The study consisted of a Screening Period of up to 28 days, admission to the clinical pharmacology unit (CPU) 1 day prior to dosing, confinement for 5 days (4 nights), followed by a 9-day non-treatment period away from the CPU (Days 5 to13), admission to CPU on Day 14 prior to dosing, confinement for 5 days (4 nights), and an End-of-Study (EOS) Visit on Day 28. Follow-up safety assessments were performed on (Days 2 through 4 and 16 through 18), and a final EOS Visit (Day 28 ± 2) occurred 10 ± 2 days after the date of discharge.

PK blood sampling for S-297995 and its metabolites was performed predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours postdose beginning on Days 1 and 15 in each sequence. PK blood sampling for cyclosporine was performed predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours postdose beginning on Day 1 in Sequence 2 and Day 15 in Sequence 1.

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Number of Subjects (Planned and Analyzed): Number of subjects planned: 14 Number of subjects enrolled: 14 Number of subjects analyzed for PK: 14 Number of subjects analyzed for safety: 14		
Diagnosis and Main Criteria for Inclusion: Health male volunteers aged between 18 and 55 years, inclusive, at the time of signing the informed consent. Body mass index ≥ 22.0 to < 30 kg/m^2 and body weight ≥ 50 kg.		
Test Product: S-297995, 0.1-mg tablets **Dose and Mode of Administration:** 0.4 mg (administered as 4 x 0.1-mg tablets) po **Lot Number:** [redacted]		
Duration of Treatment: A single dose of S-297995 0.4 mg on Days 1 and 15, alone A single dose of S-297995 0.4 mg on Days 1 and 15, with a single dose of cyclosporine 600 mg on Day 1 in Sequence 2 and Day 15 in Sequence 1		
Reference Therapy: **Product:** Cyclosporine solution USP (modified), 100 mg/mL supplied as 50 mL/bottle **Dose and Mode of Administration:** 600 mg po **Lot Number:** [redacted], expiration 11/2012		

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Criteria for Evaluation:

Pharmacokinetic Assessment:

The plasma concentration-time data were used to determine plasma PK parameters for S-297995 and its metabolites (Nor-S-297995 and S-297995-3-O-β-D-glucuronide) following dosing on Days 1 and 15 in each sequence. The blood concentration-time data were used to determine PK parameters for cyclosporine following dosing on Day 1 in Sequence 2 and Day 15 in Sequence 1.

Bioanalytic Assessment:

Plasma concentrations of S-297995 and its metabolites, Nor-S-297995 and S-297995-3-O-β-D-glucuronide, were determined by PharmaNet Canada, Inc. using a validated liquid chromatography/tandem-mass spectrometry method. The lower limits of quantification in plasma were 0.0101, 0.0403, and 0.0402 ng/mL for S-297995, Nor-S-297995, and S-297995-3-O-β-D-glucuronide, respectively.

Blood concentrations of cyclosporine were determined by PharmaNet Canada, Inc. using a validated liquid chromatography/tandem-mass spectrometry method. The lower limit of quantification in blood was 5.01 ng/mL.

Pharmacokinetic Parameters:

The WinNonlin™ computer program (WinNonlin™ Professional Network Edition, Version 5.2, [redacted]), using a standard non-compartmental analysis method, was used to obtain the following PK parameters: the maximum observed plasma or blood concentration (C_{max}), time to maximum plasma or blood concentration (T_{max}), area under the concentration-time curve from time 0 to the last measurable concentration ($AUC_{0\text{-last}}$), area under the concentration-time curve from time 0 to infinity ($AUC_{0\text{-inf}}$), apparent terminal elimination half-life ($t_{1/2,z}$), apparent elimination rate constant (λ_z), mean residence time extrapolated to infinity ($MRT_{0\text{-inf}}$), apparent total clearance (CL/F), metabolic ratio of C_{max} of metabolite to C_{max} of S-297995 (MR_{Cmax}), metabolic ratio of $AUC_{0\text{-last}}$ of metabolite to $AUC_{0\text{-last}}$ of S-297995 ($MR_{AUC0\text{-last}}$), and metabolic ratio of $AUC_{0\text{-inf}}$ of metabolite to $AUC_{0\text{-inf}}$ of S-297995 ($MR_{AUC0\text{-inf}}$).

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Safety Assessment:

Safety assessments included review of adverse events (AEs), treatment-emergent AEs (TEAEs), clinical laboratory tests (hematology, blood chemistry, and urinalysis), vital signs, 12-lead electrocardiograms (ECGs), physical examination findings, and any other parameters that were relevant for safety assessment.

Statistical Methods:

Pharmacokinetics:

In order to compare the PK of S-297995 and its metabolites when S-297995 was administered with cyclosporine to the PK when S-297995 was administered alone, an analysis of variance that considered treatment as a fixed effect and measurements within a subject as a repeated measure was performed for the following parameters of S-297995 and its metabolites: the logarithm of C_{max}, AUC, λ_z, and CL/F (S-297995 and cyclosporine only). The ratio of geometric means (GMs) and the corresponding 90% confidence interval (CI) were estimated by exponentiating the mean differences in the logarithm.

For the primary parameters, C_{max} and AUC, the 90% CIs for the ratio of GMs were provided to evaluate the effect of cyclosporine on the PK of S-297995. For Nor-S-297995 and S-297995 3-O-β-D-glucuronide, C_{max} and AUC, and the 90% CIs for the ratios of the GMs were also provided. However, for assessment of the potential interaction effects of drugs that are inhibitors of P-gp, λ_z, CL/F (S-297995 only), and the 90% CIs for the ratio of the GMs of S-297995 and its metabolites are provided for estimation and/or supplementary information.

Safety:

Due to the small sample size, no inferential statistical testing was conducted. Safety data were summarized using descriptive summaries only. All safety data were listed. The number and percentage of subjects reporting TEAEs, drug-related TEAEs (ie, TEAEs defined as possibly, probably, or definitely related to study drug), and serious AEs were summarized. Clinical laboratory data for hematology, blood chemistry, and urinalysis were summarized descriptively by time point and for the change from baseline to each post-baseline time point by treatment. Shift tables of the change relative to the normal ranges from baseline to the end of treatment are presented by treatment. Laboratory values outside the reference ranges were flagged in the data listings and a list of abnormal values is presented. Summary statistics for vital signs and ECGs are presented for each time point and for the change from baseline to each time point by treatment. Physical examination changes from baseline to each time point were summarized in shift tables by treatment. Prior and concomitant therapies were listed.

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Summary of Results:

Pharmacokinetics:

S-297995

The ratio (and the corresponding 90% CI) of the GM C_{max} of S-297995 following a single dose of S-297995 coadministered with cyclosporine compared with that following a single dose of S-297995 administered alone was 1.45 (1.27 to 1.66).

The ratio (and the corresponding 90% CI) of the GM $AUC_{0\text{-last}}$ and the $AUC_{0\text{-inf}}$ of S-297995 following a single dose of S-297995 coadministered with cyclosporine compared with that following a single dose of S-297995 administered alone were 1.79 (1.57 to 2.03) for the $AUC_{0\text{-last}}$ and 1.78 (1.57 to 2.02) for the $AUC_{0\text{-inf}}$, respectively.

The ratio (and the corresponding 90% CI) of the GM $t_{1/2,z}$ of S-297995 following a single dose of S-297995 coadministered with a single dose of cyclosporine compared with that following a single dose of S-297995 administered alone was 0.82 (0.77 to 0.88).

The ratio (and the corresponding 90% CI) of the GM CL/F of S-297995 following a single dose of S-297995 coadministered with a single dose of cyclosporine compared with that following a single dose of S-297995 administered alone was 0.56 (0.49 to 0.64).

No important difference was observed in the $MRT_{0\text{-inf}}$ of S-297995 between the 2 treatments.

The median T_{max} of S-297995 was 1.00 hour following a single dose of S-297995 coadministered with a single dose of cyclosporine which was similar to that following a single dose of S-297995 administered alone (0.75 hours).

Nor-S-297995

The ratio (and the corresponding 90% CI) of the GM C_{max} of Nor-S-297995 following a single dose of S-297995 coadministered with cyclosporine compared with that following a single dose of S-297995 administered alone was 2.56 (2.05 to 3.20).

The ratio (and the corresponding 90% CI) of the GM $AUC_{0\text{-last}}$ and the $AUC_{0\text{-inf}}$ of Nor-S-297995 following a single dose of S-297995 coadministered with cyclosporine compared with that following a single dose of S-297995 administered alone were 3.84 (3.00 to 4.91) for the $AUC_{0\text{-last}}$ and 2.48 (1.96 to 3.14) for the $AUC_{0\text{-inf}}$, respectively.

The ratio (and the corresponding 90% CI) of the GM $t_{1/2,z}$ of Nor-S-297995 following a single dose of S-297995 coadministered with a single dose of cyclosporine compared with that following a single dose of S-297995 administered alone was 1.04 (0.91 to 1.20).

No important difference was observed in the $MRT_{0\text{-inf}}$ of S-297995 between the 2 treatments.

The median T_{max} of Nor-S-297955 was later (8.02 hours) when S-297955 was coadministered

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with cyclosporine than when S-297995 was administered alone (4.00 hours).

The GM values of metabolite (Nor-S-297995) to parent (S-297995) ratios were higher (0.092, 0.264, and 0.281, for the MR_{Cmax}, the $MR_{AUC0\text{-}last}$, and the $MR_{AUC0\text{-}inf}$, respectively) when S-297955 was coadministered with cyclosporine than when S-297995 was administered alone (0.052, 0.123, and 0.201, for the MR_{Cmax}, the $MR_{AUC0\text{-}last}$, and the $MR_{AUC0\text{-}inf}$, respectively).

S-297995 3-O-β-D-glucuronide

The ratio (and the corresponding 90% CI) of the GM C_{max} of S-297995 3-O-β-D-glucuronide following a single dose of S-297995 coadministered with cyclosporine compared with that following a single dose of S-297995 administered alone was 1.83 (1.38 to 2.43).

The ratio (and the corresponding 90% CI) of the GM $AUC_{0\text{-}last}$ of S-297995 3-O-β-D-glucuronide following a single dose of S-297995 administered with cyclosporine compared with that following a single dose of S-297995 administered alone was 3.61 (2.37 to 5.50).

The median T_{max} of S-297995 3-O-β-D-glucuronide was later (5.00 hours) when S-297955 was coadministered with cyclosporine than when S-297995 was administered alone (2.5 hours).

The GM values of metabolite (S-297995 3-O-β-D-glucuronide) to parent (S-297995) ratios were higher (0.022 and 0.025, for the MR_{Cmax} and the $MR_{AUC0\text{-}last}$, respectively) when S-297955 was coadministered with cyclosporine than when S-297995 was administered alone (0.018 and 0.013, for the MR_{Cmax}, and the $MR_{AUC0\text{-}last}$, respectively), though the MR_{Cmax} and the $MR_{AUC0\text{-}last}$ for S-297995 3-O-β-D-glucuronide to S-297995 were less than 3% for the 2 treatments.

Cyclosporine

The GM C_{max} and the $AUC_{0\text{-}last}$ of cyclosporine were 1550 ng/mL and 10480 ng•hr/mL, respectively, when coadministered with S-297995. The T_{max} was at 2.00 hours.

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Safety:

- A total of 7 subjects (7/14, 50.0%) reported 20 TEAEs overall. The majority of TEAEs were reported by subjects who received S-297995 0.4 mg and cyclosporine 600 mg.
- A total of 7 subjects (7/14, 50.0%) reported 19 drug-related TEAEs; the majority of drug-related TEAEs were reported by subjects who received S-297995 0.4 mg and cyclosporine 600 mg.
- Headache (1/13, 7.7%) was the only TEAE reported in subjects who received S-297995 alone. Diarrhea (6/13, 46.2%), abdominal pain (3/13, 23.1%), nausea (3/13, 23.1%), flushing (3/13, 23.1%), frequent bowel movements (1/13, 7.7%), chills (1/13, 7.7%), hunger (1/13, 7.7%), and dizziness (1/13, 7.7%) were TEAEs reported by subjects who received S-297995 and cyclosporine.
- All TEAEs were drug-related except for hunger.
- All TEAEs and drug-related TEAEs resolved by the end of the study without sequelae.
- No deaths, serious AEs, or AEs leading to withdrawal were reported.
- No clinically significant findings in clinical laboratory evaluations, vital signs, physical examinations, or ECGs were reported.

CONCLUSIONS

Pharmacokinetics:

- There were increases in S-297995 C_{max} (45%), $AUC_{0\text{-last}}$ (79%), and $AUC_{0\text{-inf}}$ (78%) following a single dose of S-297995 coadministered with cyclosporine compared with those following a single dose of S-297995 administered alone.
- There were also increases in the C_{max} and $AUC_{0\text{-last}}$ for S-297995 metabolites, Nor-S-297995 and S-297995-3-O-β-D-glucuronide, in the presence of cyclosporine.
- The PK of cyclosporine in the presence of S-297995 was similar to the PK observed previously.

Safety:

- Although the combined administration of S-297995 0.4 mg with cyclosporine 600 mg resulted in more TEAEs than the single dose of S-297995 administered alone, a single 0.4 mg-dose of S-297995 when administered alone and in combination with cyclosporine was safe and well tolerated.
- No safety issues were identified in the study that had not been previously identified for either S-297995 or cyclosporine.

Final Report Date: 10 October 2012

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