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, Randomized, Open-label, Three-way Crossover Bioavailability Study to Evaluate the S-297995 Phase 3 Tablet Compared with the Phase 2 Tablet and the Food Effect for the Phase 3 S-297995 Tablet in Healthy Adult Subjects

Investigator and Study Center:

[redacted]

Publication (reference): None

Studied Period:

[redacted] February 2013 (first subject dosed) to
April 2013 (last subject completed)

Study Phase: Phase 1

Objectives:

The primary objectives were:

- To evaluate the single-dose relative bioavailability of the S-297995 Phase 3 tablet compared to the S-297995 Phase 2 tablet in healthy adult subjects.
- To evaluate the effect of food on the pharmacokinetics (PK) of the S-297995 Phase 3 tablet in healthy adult subjects.

The secondary objective was:

- To evaluate the safety and tolerability of S-297995 administered as a single dose of the Phase 2 tablet and the Phase 3 tablet.

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Methodology: This study was an open-label, single-dose, randomized, 3-way crossover design. The study consisted of a screening period of up to 21 days; treatment periods 1, 2, and 3, each with confinement in the clinical pharmacology unit (CPU) from Days -1 through 4 (72 hours post-dose), a 13-day washout period between periods, and an end-of-study (EOS) visit (Day 43 ± 1). The treatment sequences are shown below:

Study Treatment Sequences:

Treatment Period	**1**	**2**	**3**
Sequence 1	A	B	C
Sequence 2	B	C	A
Sequence 3	C	A	B

Treatment A = 1 x 0.2 mg S-297995 Phase 3 tablet in the fasted state
Treatment B = 2 x 0.1 mg S-297995 Phase 2 tablets in the fasted state
Treatment C = 1 x 0.2 mg S-297995 Phase 3 tablet in the fed state

Prospective subjects were screened beginning 21 days prior to the first planned dose of S-297995. Eligible subjects were randomized on Day -1 of Treatment Period 1 to 1 of 3 regimens, Sequence 1, 2, or 3.

Subjects received all regimens in a crossover fashion according to their randomized sequence. For each treatment period, admission to the CPU began the day before dosing (Days -1, 14, and 28) and continued for a minimum of 72 hours post-dose (through Day 4, Day 18, and Day 32, respectively).

On the morning of the dosing day of each treatment period (Days 1, 15, and 29), subjects received either two 0.1 mg tablets (Phase 2) or a 0.2 mg tablet (Phase 3) of S-297995 orally. Subjects were dosed in the fasted or fed state in each treatment period as determined by the sequence to which they were randomized. Subjects fasted for 10 hours prior to receiving either the 2 x 0.1 mg tablets (Phase 2) or 1 x 0.2 mg tablet (Phase 3) of S-297995 in the fasted state and remained fasting until 4 hours post-dose, when lunch was provided. Subjects, who received 1 x 0.2 mg tablet (Phase 3) of S-297995 in the fed state, fasted 10 hours and received a Food and Drug Administration (FDA)-standardized high-fat/high-calorie breakfast 30 minutes prior to dosing. Breakfast was to have been consumed in 30 minutes or less, and no food was allowed for at least 4 hours post-dose, when lunch was provided.

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For all treatment periods, meals were identical throughout each period with the exception of breakfast when subjects received the FDA-standardized high-fat/high-calorie breakfast in the fed condition. Water was allowed ad libitum during confinement except for 1 hour before or 2 hours post-dose.

During each treatment period, blood samples for PK analysis of plasma S-297995 concentrations were collected prior to dosing 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 post-dose.

Number of Subjects (Planned and Analyzed):

A total of 18 subjects was planned to enter the study, so that at least 12 subjects would complete the study. Eighteen subjects were enrolled and each subject received at least 1 dose of the study drug. A total of 14 subjects completed all sequences per protocol.

Diagnosis and Main Criteria for Inclusion:

Healthy males and females as determined by medical history, physical examination, vital signs, electrocardiogram (ECG), and clinical laboratory tests, ≥ 18 to ≤ 50 years of age, with a body mass index between ≥ 18 to ≤ 30 (kg/m^2), and a body weight ≥ 50 kg.

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

S-297995, 0.1 mg tablet, administered orally, lot No. [redacted]
S-297995, 0.2 mg tablet, administered orally, lot No. [redacted]

Subjects were randomly assigned to 1 of 3 treatment sequences (ABC, BCA, and CAB). Treatments were:

- A 1 × 0.2 mg S-297995 Phase 3 tablet in the fasted state
- B 2 × 0.1 mg S-297995 Phase 2 tablets in the fasted state
- C 1 × 0.2 mg S-297995 Phase 3 tablet in the fed state

Duration of Treatment:

For each of 3 treatment periods, subjects received the study drug on Day 1, followed by 13 days without treatment. The total length of the study including screening and the final post-treatment assessment was approximately 64 days.

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Reference Therapy: Not applicable		

Criteria for Evaluation:

Pharmacokinetic Analysis:

Blood samples were obtained for PK analysis.

Bioanalytical Assessment:

- Measurement method: Liquid chromatography/tandem mass spectrometry
- Lower limit of quantification of S-297995 in plasma: 0.0100 ng/mL
- Lower limit of quantification of Nor-S-297995 in plasma: 0.0400 ng/mL

Pharmacokinetic Parameters:

Individual plasma concentrations of S-297995 and Nor-S-297995 were listed and summarized by treatment and by nominal sampling time with number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), and coefficient of variation expressed as a percentage (CV%, calculated by SD/mean x 100), geometric mean, and coefficient of variation for geometric mean (CV% geometric mean); and median, minimum, and maximum values at each sampling time. The PK parameters are shown below:

Bioavailability Determination:

Primary: C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$
Secondary: T_{max}, λ_z, $t_{1/2,z}$, CL/F, and MRT

Food Effect Determination:

Primary: C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$
Secondary: T_{max}, λ_z, $t_{1/2,z}$, CL/F, and MRT

Abbreviations: $AUC_{0\text{-inf}}$ = area under the concentration-time curve extrapolated to infinity; $AUC_{0\text{-last}}$ = area under the concentration-time curve from zero to time of the last measurable concentration; CL/F = apparent total clearance; C_{max} = maximum observed plasma concentration; MRT = mean residence time; λ_z = apparent terminal elimination rate constant; $t_{1/2,z}$ = apparent terminal elimination half-life; T_{max} = time to maximum observed plasma concentration.

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Safety Assessment:

Safety was assessed by monitoring of clinical laboratory evaluations (including hematology and blood chemistry tests, and urinalysis), vital signs, 12-lead ECGs, and physical examinations. Adverse events (AEs) were collected, and treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs) and serious adverse events (SAEs) were tabulated.

Statistical Methods:

Pharmacokinetics:

Bioavailability

In the crossover study, analysis of variance (ANOVA) was performed for ln-transformed values for C_{max}, $AUC_{0\ last}$, $AUC_{0\ inf}$, λ_z, $t_{1/2,z}$, CL/F, and MRT of S-297995 including terms for subject as a random effect, and tablet, treatment sequence and period, as fixed effects by using SAS Proc Mixed.

The point estimates and 90% confidence intervals (CI) to compare the PK parameters for each formulation were constructed using the error variance obtained from the ANOVA. The point estimates and 90% CI were then back-transformed to give estimates for the ratio of the parameters in the administration of 1 × 0.2 mg tablet to that of 2 × 0.1 mg tablets.

Food Effect

In the crossover study, ANOVA was performed for ln-transformed values for C_{max}, $AUC_{0\ last}$, $AUC_{0\ inf}$, λ_z, $t_{1/2,z}$, CL/F, and MRT of S-297995 including terms for subject as a random effect and food condition, treatment sequence and period, as fixed effects by using SAS Proc Mixed.

The point estimates and 90% CI to compare the PK parameters for each food condition were constructed using the error variance obtained from the ANOVA. The point estimates and 90% CI were then back-transformed to give estimates for the ratio of the parameters in the fed state to fasted state.

Safety:

Due to the small sample sizes, no inferential statistical testing was conducted. Safety data were summarized using descriptive statistics only. The Safety Population was used for all safety analyses. All safety data are listed.

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Summary of Results:

Subject Disposition:

Eighteen subjects were enrolled into the study. Fourteen subjects completed all sequences per protocol. Fifteen subjects received Treatment A, 16 subjects received Treatment B, and 18 subjects received Treatment C. All 18 subjects, each of whom received at least 1 dose of the study drug, were included in the Safety, PK Concentration, and PK Parameter Populations.

Pharmacokinetics:

Relative Bioavailability and Food Effect:

The descriptive summary and statistical analysis of S-297995 PK parameters follows:

Summary of S-297995 Pharmacokinetic Parameters and Statistical Analysis of Bioavailability and Food Effect

Parameter	Treatment	N	Geometric Mean (CV% Geometric Mean)[a]	A/B Least Squares Geometric Mean Ratio (90% CI)[b]	C/A Least Squares Geometric Mean Ratio (90% CI)[c]
C_{max}	A	15	3.07 (18.7)	1.1328 (1.0183, 1.2602)	
(ng/mL)	B	16	2.74 (26.6)		
	C	18	2.01 (19.0)	0.6488	(0.5846, 0.7200)
$AUC_{0\text{-last}}$	A	14	23.51 (17.0)	1.0446 (1.0006, 1.0905)	
(ng•hr/mL)	B	16	22.43 (16.7)		
	C	18	22.84 (13.9)		0.9677 (0.9266, 1.0106)
$AUC_{0\text{-inf}}$	A	14	23.79 (17.1)	1.0444 (1.0008, 1.0899)	
(ng•hr/mL)	B	16	22.70 (16.7)		
	C	18	23.13 (14.0)		0.9683 (0.9276, 1.0109)
T_{max} (hr)	A	15	0.75 (0.50, 2.00)	NA	
	B	16	0.75 (0.50, 2.03)		
	C	18	2.50 (0.75, 5.02)		NA

NA: Not applicable

a. T_{max} is presented as median (range).
b. The analysis is based on the analysis of variance model: ln (Parameter) = Subject + Tablet + Sequence + Period + Random error, where subject is a random effect, tablet, sequence, and period are fixed effects

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and Random error is a random residual error. Results are exponentiated to present geometric mean ratios.

c. The analysis is based on the analysis of variance model: ln (Parameter) = Subject + Food condition + Sequence + Period + Random error, where subject is a random effect, food condition, sequence, and period are fixed effects and Random error is a random residual error. Results are exponentiated to present geometric mean ratios.

Treatment A = 1 x 0.2 mg S-297995 Phase 3 tablet in the fasted state
Treatment B = 2 x 0.1 mg S-297995 Phase 2 tablets in the fasted state
Treatment C = 1 x 0.2 mg S-297995 Phase 3 tablet in the fed state

Source: Table 14.2.1.3, Table 14.2.1.5, Table 14.2.1.6

Pharmacokinetics of Nor-S-297995:

The descriptive summary of Nor-S-297995 PK parameters follows:

Summary of Nor-S-297995 Plasma Pharmacokinetic Parameters

Parameter	Treatment	N	Geometric Mean (CV% Geometric Mean)[a]
C_{max} (ng/mL)	A	15	0.146 (35.7)
	B	16	0.146 (22.0)
	C	18	0.112 (27.2)
$AUC_{0\text{-last}}$ (ng•hr/mL)	A	14	2.457 (95.1)
	B	16	2.780 (43.2)
	C	18	2.044 (63.2)
T_{max} (hr)	A	15	4.00 (3.00, 10.00)
	B	15	4.00 (4.00, 8.00)
	C	17	8.00 (4.00, 12.10)

a. T_{max} is presented as median (range).

Note: $AUC_{0\text{-inf}}$ of Nor-S-297995 was not summarized due to insufficient data points to characterize a linear terminal phase for all profiles.
Treatment A = 1 x 0.2 mg S-297995 Phase 3 tablet in the fasted state
Treatment B = 2 x 0.1 mg S-297995 Phase 2 tablets in the fasted state
Treatment C = 1 x 0.2 mg S-297995 Phase 3 tablet in the fed state

Source: Table 14.2.1.4

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Safety:

- There were no deaths or SAEs.
- One subject discontinued from study prematurely due to a TEAE of feeling hot which was mild and not related to the study drug.
- Ten subjects reported at least 1 TEAE; overall, 17 TEAEs were reported:
  - 5 subjects with 5 TEAEs in Treatment A
  - 2 subjects with 3 TEAEs in Treatment B
  - 5 subjects with 9 TEAEs in Treatment C
- All TEAEs were mild or moderate in severity and all resolved by the end of study.
- Four subjects reported 7 TEAEs considered possibly related to the study drug:
  - Subject [redacted] with headache, dizziness, and nausea
  - Subject [redacted] with headache and nausea
  - Subject [redacted] with headache
  - Subject [redacted] with blurred vision
- Most frequently reported TEAEs (≥ 2 subjects in any treatment) were:
  - Headache in 3 subjects in Treatment C
  - Ear pain in 2 subjects in Treatment A
  - Nausea in 2 subjects in Treatment C
- Three TEAEs were associated with abnormal laboratory results (urinary tract infection, anemia, and hematuria) and none of these 3 events was considered related to the study drug.
- There were no clinically significant findings in other laboratory results, vital signs, ECGs, or physical examinations.

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CONCLUSIONS

Pharmacokinetics:

- Under fasted conditions, the C_{max} of S-297995 was slightly higher (13%) for the S-297995 Phase 3 tablet compared with the Phase 2 tablet. The $AUC_{0\ last}$ and $AUC_{0\ inf}$ were equivalent, and T_{max} was the same (0.75 hour) for the 2 formulations.
- S-297995 C_{max} was reduced by 35% when the S-297995 Phase 3 tablet was administered following a high-fat/high-calorie meal; however, no food effect was observed for $AUC_{0\ last}$ or $AUC_{0\ inf}$. The T_{max} was prolonged from 0.75 hour in the fasted state to 2.50 hour in the fed state.

Safety:

- S-297995 administered as a single dose of the Phase 2 tablet and as a single dose of the Phase 3 tablet with or without food was safe and well tolerated in healthy male and female subjects. No adverse events or changes in laboratory values were identified in this study that had not been previously identified for S-297995 in earlier studies.

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