2. Synopsis

English Translation (The original report was written in Japanese)

Name of Sponsor: Shionogi & Co., Ltd.	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Not determined	**Volume:**	
Name of Active Ingredient: S-297995	**Page:**	

Study Title:
An open-label, crossover study to assess the bioavailability and the food effect on the pharmacokinetics of a single dose of S-297995 in healthy Japanese adult males

Investigator: [redacted]

Study Center: [redacted]

Publication (reference): None

Studied Period: 2 months
From May [redacted], 2009 (the first subject dosed the study drug)
to June [redacted], 2009 (the last subject completed)

Phase of Development: Phase 1

Objectives
Primary objective:
To compare the pharmacokinetics of S-297995 between solution and tablet formulations following a single oral 10 mg dose administration to healthy Japanese adult male subjects, and to assess the effect of drug-food interaction on the bioavailability of the tablet.
Secondary objective:
To evaluate the safety and tolerability of S-297995 following a single oral dose administration.

Methodology
The solution or tablet containing 10 mg of S-297995 was administered to 15 healthy Japanese adult male subjects (5 subjects/cohort × 3 cohorts). In each cohort a single oral dose of the study drug was administered in each period in the sequence shown below under one of the administration conditions (solution/fasted, tablet/fasted, tablet/fed), with a washout period of 6-days.

Using the crossover method, the adverse events and adverse drug reactions, and the pharmacokinetic parameters were compared.

Cohort	1st period	2nd period	3rd period
1	Solution/Fasted	Tablet/Fasted	Tablet/Fed
2	Tablet/Fasted	Tablet/Fed	Solution/Fasted
3	Tablet/Fed	Solution/Fasted	Tablet/Fasted

Endpoints

(1) Adverse events (AEs) and adverse drug reactions (ADRs) which occurred after administration of the study drug
(2) Abnormal changes in laboratory values (hematology tests, blood chemistry tests, endocrinological test, and urinalysis)
(3) Changes from baseline in vital signs (blood pressures, pulse rate, respiratory rate, and body temperature) and electrocardiogram (ECG)
(4) Pharmacokinetic parameters

Number of Subjects (Planned and Analyzed)

Target number of subjects: 15 (5 subjects/cohort × 3 cohorts)
Number of subjects randomized: 15 (5 subjects/cohort × 3 cohorts)
Number of subjects administered:15
Number of subjects in the pharmacokinetic analysis population: 15
Number of subjects in the safety analysis population: 15

Diagnosis and Main Criteria for Inclusion

1. Inclusion criteria

(1) Subjects who can provide a signed and dated written informed consent form for voluntary participation in the study prior to screening
(2) Subjects ≥ 20 and < 40 years of age (at the time of agreement to informed consent)
(3) Japanese male volunteers considered healthy based on screening assessment
(4) Body weight of ≥ 50 to ≤ 80 kg and body mass index (BMI) of ≥ 18.5 to < 25.0, as calculated from body weight (kg) / (height [m])^2

2. Exclusion criteria

(1) Use of any drug (eg, prescription drugs, over-the-counter drugs, Chinese medicines, other supplements, vitamin preparations) within 3 days before screening or 1 week before admission
(2) Use of any drug containing opioids (eg, codeine, other antitussives) between 2 weeks before screening and admission

(3) Use of any medication known to be inhibitors (eg, itraconazole) or inducers (eg, rifampicin) of the cytochrome P450 drug-metabolizing system between 4 weeks before screening and admission
(4) Smoking or consumption of any smoking-cessation aids containing nicotine between 24 weeks before screening and admission
(5) In a supine position, systolic blood pressure is ≥ 140 mm Hg or < 90 mm Hg, diastolic blood pressure is ≥ 90 mm Hg or < 40 mm Hg, or pulse rate is ≥ 90 bpm or < 40 bpm.
(6) Abnormal ECG findings considered inappropriate for the study by the investigator/subinvestigator
(7) Presence of any chronic disease that requires pharmacotherapy or other treatments (eg, diet restriction, physical therapy)
(8) History of chronic abnormal bowel movements (eg, chronic constipation, chronic diarrhea, irritable bowel syndrome)
(9) History of hypersensitivity likely associated with a drug or of serious adverse drug reactions
(10) Presence or history of allergic symptoms (including food allergy, but with the exception of inactive pollinosis)
(11) History of alcohol or drug dependency
(12) Positive result in urine screening tests for drug abuse
(13) Presence or history of hepatic disorder
(14) Presence or history of any neurological, gastrointestinal, renal, cardiovascular, psychiatric, respiratory, metabolic, endocrine, hematological, or other clinical important diseases, considered inappropriate for the study by the investigator/subinvestigator
(15) Surgical history of gastric, vagus nerve, or intestinal resection, etc (except for appendicitis)
(16) Blood donation of > 400 mL within 12 weeks before screening, or of > 200 mL within 4 weeks before screening, or blood collection or donation of any amount between screening and admission
(17) Use of other investigational products within 16 weeks before admission
(18) Noncompliance with the individual requirements in section "Management of subjects" of the study protocol
(19) Positive results in any of the following tests: serological test for syphilis, HBs antigen, HCV antibody, or HIV antigen/antibody
(20) Previously received S-297995
(21) Considered ineligible for the study by the investigator/subinvestigator

Test Product, Dose and Mode of Administration, Lot Number

1. Test Drug (S-297995)
Solution or tablet containing 10 mg of S-297995

2. Dosage
The solution or tablet containing 10 mg of S-297995 was administered once daily

3. Method of Administration
A single oral dose of 10 mg of the study drug was administered either in the fasted or in the fed states.

4. Lot Number (Manufacturing Number)
S-297995 bulk drug for preparation of solution; [redacted]
S-297995 10-mg tablet; [redacted]

Control Drug, Dose and Mode of Administration, Lot Number

No control drug was used in the study.

Duration of Treatment: One day × 3 times

Criteria for Evaluation

1. Pharmacokinetic Evaluation

The plasma concentrations (unchanged S-297995, Nor-S-297995, S-297995 3-*O*-β-D-glucuronide, S-297995 6-*O*-β-D-glucuronide, and Benzamidine) were measured at planned sampling time point after a single 10 mg dose of S-297995. Pharmacokinetic parameters (maximum plasma concentration [Cmax], time to reach maximum plasma concentration [Tmax], area under the plasma concentration-time curve [AUC], elimination half-life [$t_{1/2,z}$], and mean residence time [$MRT_{0\text{-}inf}$]) were calculated from the data on plasma concentrations. The respective pharmacokinetic parameters were compared to investigate the effect of formulation and the effect of drug-food interaction.

2. Safety Evaluation

Symptoms and signs, laboratory tests (hematology, blood chemistry, endocrinological tests, and urinalysis), vital signs (blood pressure, heart rate, respiration rate, and body temperature), and ECG were examined to assess the presence or absence of adverse events. For each adverse event, the causal relationship to the study drug was assessed based on the following information: the time of onset, time of disappearance, severity, action taken, and outcome.

Statistical Methods

1. Pharmacokinetic Analysis

The effect on formulation on the pharmacokinetics of S-297995 was examined after a single oral 10 mg dose of S-297995. In addition, the effect of drug-food interaction on pharmacokinetics was investigated after administration of the tablet. The geometric means and 90% confidence intervals of the geometric mean ratios were also calculated for the Cmax, AUC, $t_{1/2,z}$ and $MRT_{0\text{-inf}}$.

2. Safety Analysis

The frequencies of adverse events and adverse drug reactions were calculated and the 95% confidence interval of the incidence was calculated using the Clopper-Pearson method. The number of events (of adverse events or adverse drug reactions) and incidence of subjects experiencing adverse events or adverse drug reactions were counted according to System Organ Class and Preferred Term. The number of subjects, incidence, and number of events in each category regarding severity, seriousness, action taken with the study drug, concomitant or additional treatment, outcome, and causal relationship with the study drug were classified. Laboratory tests, vital signs, and ECG tests were performed over time, and the descriptive statistics and frequencies of abnormal values were calculated from the data. For urinalysis (qualitative), the frequencies of abnormal values were calculated.

Summary of Results

Pharmacokinetics

- The tablet/solution ratios (90% confidence interval) of the geometric means for the pharmacokinetic parameters after 10 mg dose of S-297995 administered in the fasted state were as follows: 0.909 (0.775-1.07) for Cmax, 0.980 (0.940-1.02) for $AUC_{0\text{-last}}$, 0.980 (0.941-1.02) for $AUC_{0\text{-inf}}$. The median Tmax was 0.50 hours for the solution and 0.75 hours for the tablet. Cmax having not met the criteria for bioequivalence, no large differences were found in pharmacokinetic parameters between the solution and the tablet.
- The fed/fasted ratios of the geometric means (90% confidence interval) for the pharmacokinetic parameters after a single oral dose of a 10 mg S-297995 tablet were as follows: 0.806 (0.687-0.945) for Cmax, 0.951 (0.913-0.990) for $AUC_{0\text{-last}}$, 0.951 (0.913-0.990) for $AUC_{0\text{-inf}}$. The median Tmax was 0.75 hours in the fasted state and 1.5 hours in the fed state. In the fed state, absorption of S-297995 was delayed and the Cmax decreased by 20% as compared with those in the fasted state, indicating that the pharmacokinetic profiles of S-297995 were different between in the fasted and the fed states, though the drug-food interaction was small.

• The geometric mean $AUC_{0\text{-inf}}$ ratio of Nor-S-297995 to unchanged S-297995 (MR_{AUC}) ranged from 20.1% to 24.0% under the conditions of administration tested. The geometric mean $t_{1/2,z}$ for Nor-S-297995 was 17.0 to 17.8 hours, and this was longer than that of 10.4 to 11.4 hours for unchanged S-297995. The geometric mean MR_{AUC} for the S-297995 3-*O*-β-D-glucuronide and S-297995 6-*O*-β-D-glucuronide relative to unchanged S-297995 were 2% or less and 0.1% or less, respectively. The plasma concentration of Benzamidine was below the limit of quantitation (0.300 ng/mL) at almost all measurement points.

	N	Cmax [a] (ng/mL)	Tmax [b] (hr)	$AUC_{0\text{-last}}$ [a] (ng·hr/mL)	$AUC_{0\text{-inf}}$ [a] (ng·hr/mL)	$t_{1/2,z}$ [a] (hr)	$MRT_{0\text{-inf}}$ [a] (hr)
Solution/Fasted	14	186 (29.4)	0.50 (0.25, 2.5)	1041 (19.1)	1045 (19.1)	11.1 (10.4)	8.92 (14.7)
Tablet/Fasted	15	169 (26.4)	0.75 (0.50, 4.0)	1020 (17.9)	1025 (17.9)	11.4 (12.2)	9.14 (15.5)
Tablet/Fed	14	136 (31.4)	1.5 (0.50, 4.0)	968.6 (22.6)	972.9 (22.6)	10.4 (10.2)	10.1 (14.9)

[a] Geometric mean (CV% of geometric mean)
[b] Median (Min, Max)

Safety

	Solution/Fasted	Tablet/Fasted	Tablet/Fed
Safety analysis population	14	15	14
Subjects with any AE	2	3	1
Number of AE	2	3	1
%	14.3	20.0	7.1
AE (PT)			
Gastroenteritis bacterial	1 (1)	0 (0)	0 (0)
	(7.1)	0.0%	0.0%
Blood prolactin increased	1 (1)	3 (3)	0 (0)
	(7.1)	(20.0)	0.0%
Alanine aminotransferase	0 (0)	0 (0)	1 (1)
increased	0.0%	0.0%	(7.1)

Note: This table includes the number of subjects (the number of events) and percentage of subjects with AEs.

• Two AEs were reported in 2 of 14 subjects in the solution/fasted group, 3 AEs were reported in 3 of 15 subjects in the tablet/fasted group, and 1 AE was reported in 1 of 14 subjects in the tablet/fed group. One ADR was reported in 1 of 14 subjects in the solution/fasted group, 3 ADRs were reported in 3 of 15 subjects in the tablet/fasted group, and no ADRs were reported in the tablet/fed group.
• The following AEs were reported: 1 event each of gastroenteritis bacterial and blood prolactin increased in 1 of 14 subjects in the solution/fasted group, 3 events of blood

prolactin increased in 3 of 15 subjects in the tablet/fasted group, and 1 event of alanine aminotransferase increased in 1 of 14 subjects in the tablet/fed group. Only gastroenteritis bacterial with additional treatment was moderate, and the other events were mild. All AEs were resolved. With respect to a causal relationship with the study drug, all events of blood prolactin increased were considered as ADRs, and the other events were considered unrelated. No AEs were found on the day of the initiation of administration (Day 1) under all administration conditions, and most AEs occurred on 3 days after the initiation of administration (Day 3) or later.

- Blood prolactin increased was found in 4 subjects (1 in the solution/fasted group, 3 in the tablet/fasted group). All occurred only in the 1st period of the study, and all were considered as ADRs. Among these, in 1 subject (subject ID code: [redacted]) experienced no symptoms, signs, and abnormal laboratory test values other than blood prolactin. The blood prolactin concentrations of the subjects had not returned to baseline by Day 4, and the subject was thereby withdrawn from the study at the end of the 1st period. However, the blood prolactin concentrations had returned to baseline without concomitant or additional treatment by the postdosing examination (Day 7). In the other 3 subjects, the blood prolactin concentrations had returned to baseline by Day 4 without any corrective action.
- No deaths or other serious adverse events were reported. Other significant AEs 1 subject with gastroenteritis bacterial in the solution/fasted group and 1 subject with blood prolactin increased in the tablet/fasted group were reported. Gastroenteritis bacterial was considered moderate due to concomitant or additional treatment, but a causal relationship with the study drug was denied. Although the blood prolactin concentrations had not returned to baseline by Day 4, the concentration had returned to baseline without any concomitant or additional treatment by the postdosing examination (Day 7). Therefore, the event was considered mild. All of the AEs were resolved, hence they were not considered clinically significant.
- No clinically significant abnormalities were found in the vital signs and ECG.

From these, a single 10 mg dose of S-297995 is safe and well-tolerated under the administration conditions of solution/fasted, tablet/fasted, and tablet/fed.

CONCLUSIONS

With respect to pharmacokinetics, Cmax having not met the criteria for bioequivalence, no large differences were found in pharmacokinetic parameters between the solution and the tablet. In the fed state, absorption of S-297995 was delayed and the Cmax decreased by 20% as compared with those in the fasted state, indicating that the pharmacokinetic profiles

of S-297995 were different between in the fasted and the fed states, though the drug-food interaction was small. On the other hand, with respect to safety no significant differences in the type of events, number of events, severity, and outcome of AEs that appeared after administration were found between administration conditions, and no clinically significant AEs were found in the study. A single oral dose of 10 mg S-297995 is safe and well-tolerated under all the administration conditions of solution/fasted, tablet/fasted, and tablet/fed.
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