

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: Phase 1 single dose clinical study of S-297995 in healthy Japanese adult males		
Investigator: [REDACTED]		
Study Center: [REDACTED]		
Publication (reference): None		
Studied Period: 3 months From February [REDACTED], 2009 (the first subject dosed the study drug) to April [REDACTED], 2009 (the last subject completed)		
Phase of Development: Phase 1		
Objectives To evaluate the safety, tolerability, and pharmacokinetics of single oral doses of S-297995 in healthy Japanese adult males in a randomized, double-blind, placebo-controlled manner		
Methodology The healthy Japanese adult male subjects were randomized to 7 single dose groups of S-297995 (S-297995, 6; placebo, 2); 0.1 mg (0.1-mg group), 0.3 mg (0.3-mg group), 1 mg (1-mg group), 3 mg (3-mg group), 10 mg (10-mg group), 30 mg (30-mg group), 100 mg (100-mg group) or placebo (pooled placebo group). Within each group of 8 subjects, 6 subjects received S-297995 and 2 subjects received matching placebo orally once daily to evaluate the safety and pharmacokinetics of S-297995. The initial dose was 0.1 mg. The dose was increased up to 100 mg stepwise while monitoring the safety of subjects in each step. The numbers of adverse events (AEs) and adverse drug reactions (ADRs) were counted and pharmacokinetic parameters were calculated at each dose. In the 0.1-mg group (Step 1) 4 subjects received the study drug on the first day. After confirming the safety of this dose, the remaining 4 subjects received the study drug on the		

following day.

Study Schedule

	Screening	Hospitalization						Posttreatment assessment
		Admission (Day 1)	Day 1 (Immediately before dosing)	Day 1 (At dosing)	Day 1 (After dosing)	Day 2 (24 hrs postdosing)	Day 2 (At discharge)	Day 5
Informed consent	X							
Background factors	X	X						
Confirmation of the inclusion and exclusion criteria	X	X						
Assignment			X					
Study medication				X				
Symptoms and signs	X	X	X		X ^{a)}	X	X	X
Adverse events					←————→			
Immunological tests	X							
Urine screening tests for drug abuse	X	X						
Vital signs	X	X	X		X ^{b)}	X ^{c)}		X ^{c)}
Hematology test	X	X	X			X		X
Blood chemistry tests	X	X	X			X		X
Blood coagulation test	X							
Urinalysis	X	X	X			X		X
ECG	X	X	X		X ^{d)}	X		X
Blood sampling for measurement of plasma drug concentration			X		X ^{e)}	X ^{e)}	X ^{e)}	
Urine sampling for measurement of urine drug concentration ^{f)}			X		←————→			

- a) Observation of symptoms and signs postdosing on Day 1 was performed at 1, 2, 4, 8 and 12 hours after dosing.
- b) Checking of vital signs postdosing on Day 1 was performed at 1, 2, 4, 6 and 12 hours after dosing.
(Blood pressure in a standing position was performed only at 1 and 2 hours after dosing)
- c) Blood pressure in a standing position was unnecessary.
- d) ECG postdosing on Day 1 was performed at 1, 2, 4, 6 and 8 hours after dosing.
- e) Blood sampling times for drug concentration measurement: At 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24 and 32 hours after dosing
- f) For drug concentration measurement in urine, 0 6 hour, 6 12 hour and 12 24 hour postdosing urine was collected.

Endpoints

- 1) AEs and ADRs that occurred after administration of the study drug
- 2) Abnormal changes in laboratory values (hematology tests, blood chemistry tests and urinalysis)

3) Changes in vital signs (supine and standing blood pressures, pulse rate, respiratory rate and body temperature) and ECG before and after dosing

4) Pharmacokinetic parameters

Number of Subjects (Planned and Analyzed)

Target number of subjects: 56

Number of subjects randomized: 56

Number of subjects administered: 42 in the S-297995 group and 14 in the placebo group

Number of subjects in the pharmacokinetic analysis set: 42 (in the S-297995 group)

Number of subjects in the safety analysis set: 56 (n=42 in the S-297995 group and n=14 in the placebo group)

Diagnosis and Main Criteria for Inclusion

1. Inclusion criteria

- 1) Subjects who can provide a signed and dated written informed consent to voluntary participation in the study prior to screening
- 2) Subjects of ≥ 20 and < 40 years of age (at the time of agreement to informed consent)
- 3) Japanese male volunteers considered healthy based on screening examination
- 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 herbal medicines, and other supplements or vitamin preparations) within 3 days before screening or 1 week before admission
- 2) Use of any drug containing opioids (eg, codeine and 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, the systolic blood pressure is ≥ 140 mm Hg or < 90 mm Hg, the diastolic blood pressure is ≥ 90 mm Hg or < 40 mm Hg, or heart rate is ≥ 90 bpm or < 40 bpm.
- 6) In a standing position, the systolic blood pressure is decreased by ≥ 20 mm Hg or the diastolic blood pressure is decrease by ≥ 10 mm Hg, compared to the blood pressure in a supine position, or a history of orthostatic hypotension.
- 7) Abnormal ECG findings considered inappropriate for the study by the

- investigator/subinvestigator
- 8) Presence of any chronic disease that requires pharmacotherapy or other treatments (eg, diet restriction, physical therapy)
 - 9) History of chronic abnormal bowel movements (eg, chronic constipation, chronic diarrhea, irritable bowel syndrome)
 - 10) History of hypersensitivity likely associated with a drug or of serious adverse drug reactions
 - 11) Presence or history of allergic symptoms (including food allergy, but with the exception of inactive pollinosis)
 - 12) History of alcohol or drug dependency
 - 13) Positive result for urine screening tests for drug abuse
 - 14) Presence or history of hepatic disorder
 - 15) 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
 - 16) Surgical history of gastric, vagus nerve, or intestinal resection, etc (except for appendicitis)
 - 17) Blood donation of > 400 mL within 12 weeks before screening or of > 200 mL within 4 weeks before screening; or blood collection or blood donation between screening and admission
 - 18) Use of other investigational products within 16 weeks before admission
 - 19) Noncompliance with the individual requirements in section “[Management of subjects](#)” of the study protocol
 - 20) Positive results on any of the following tests: serological tests for syphilis, HBs antigen, HCV antibody, or HIV antigen/antibody
 - 21) Ineligible for the study considered by the investigator/subinvestigator

Test Product, Dose and Mode of Administration, Lot Number

1. Test Drug (S-297995)

A solutions containing S-297995 monotosylate for 0.1- to 30-mg groups

A suspension containing S-297995 monotosylate for 100-mg group

(solution/suspension, hereinafter)

2. Dosage

A solution/suspension containing 0.1, 0.3, 1, 3, 10, 30 or 100 mg of S-297995 was administered once daily in the fasted state.

3. Method of Administration

After preparation of the solution/suspension, the person responsible for study drug assignment provided each subject with 60 mL of the randomized solution/suspension. After dosing, 60 mL of Water for Injection, JP were placed in the glass container (brown bottle) used for dosing. The whole contents were administered. The procedure was repeated twice (120 mL in total).

4. Lot Number (Manufacturing Number)

S-297995 bulk drug for preparation of solution/suspension; [REDACTED]

Control Drug, Dose and Mode of Administration, Lot Number

1. Control Drug

A solutions containing the placebo of S-297995 monotosylate for 0.1- to 30-mg group
A suspension containing the placebo of S-297995 monotosylate for 100-mg group
(solution/suspension, hereinafter)

2. Dosage

Placebo solution/suspension was administered in the same volume as that of the test solution/suspension once daily in the fasted state.

3. Method of Administration

The subjects received formulated placebo solution/suspension according to the method of the administration of the test drug.

Duration of Treatment: One day

Criteria for Evaluation

1. Pharmacokinetic Evaluation

The pharmacokinetic parameters (C_{max} [ng/mL], T_{max} [hr], $t_{1/2,z}$ [hr], AUC [ng·hr/mL], CL/F [L/hr] and $Ratio_{AUC}$ [the ratio of the AUC_{inf} for metabolite to that for unchanged S-297995]) and urinary excretion rates (%) of unchanged S-297995 and its metabolites (nor-S-297995, S-297995 3-*O*- β -D-glucuronide, S-297995 6-*O*- β -D-glucuronide, and Benzamidine) were compared among the S-297995 groups.

1) Plasma concentrations of unchanged S-297995 and its metabolites immediately prior to dosing and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24 and 32 hours postdosing

2) Urinary concentrations of unchanged S-297995 and its metabolites immediately prior to dosing and at 0-6, 6-12 and 12-24 hours postdosing

2. Safety Evaluation

Symptoms and signs were investigated before and after dosing (or at the time of withdrawal from the study or during the study drug administration). Laboratory tests (hematology tests, blood chemistry tests and urinalysis) were performed to investigate adverse events. Vital signs (supine and standing blood pressures, pulse rate, respiratory rate and body temperature) and ECG were measured to examine changes before and after dosing. Each adverse event was investigated for the date of onset, severity, action taken, outcome, date of outcome and its causal relationship with the study drug according to the following criteria (classification of causal relationship and the definitions) to observe ADRs.

Classification of causal relationship and the definitions

According to the following definitions, a causal relationship of each adverse event with the study drug was assessed in 4 grades. Events assessed other than “4. Not related” were classified as ADRs.

1. Definitely related: There is a reasonable temporal relationship between administration of the study drug and occurrence of the adverse event, and there are no other causative factors than the study drug that can explain the event.
2. Probably related: Involvement of other causative factors than the study drug is unlikely.
3. Possibly related: Involvement of other causative factors than the study drug can be considered, but a causal relationship with the study drug cannot be ruled out.
4. Not related: The event can be clearly explained by a causative factor other than the study drug, or there is no reasonable temporal relationship between administration of the study drug and occurrence of the adverse event.

For any adverse event occurring, the highest degree of its severity during its course was recorded using the 3-grade scale defined below.

1. Mild: A symptom or sign is present, but does not interfere with the subject’s daily activities and does not require treatment.

2. Moderate: An event that interferes with the subject's daily activities because of discomfort, or affects the clinical condition and requires treatment.
3. Severe: An event by which the subject is unable to conduct daily activities and significant clinical influence is observed.

Statistical Methods

1. Pharmacokinetic Analysis

Based on the plasma and urinary drug concentration data, the pharmacokinetic parameters (C_{max} [ng/mL], T_{max} [hr], $t_{1/2,z}$ [hr], AUC [ng·hr/mL], CL/F [L/hr] and $Ratio_{AUC}$) and urinary excretion rates (%) of unchanged S-297995 and its metabolites were calculated for each S-297995 group. In addition, each of the pharmacokinetic parameters of unchanged S-297995 was examined for its dose-dependency.

2. Safety Analysis

The incidences of AEs and ADRs were assessed by severity, seriousness, action taken, outcome and relationship. Vital signs (supine and standing blood pressures, pulse rate, respiratory rate and body temperature) and ECG were recorded over time through the course of the study. The summary statistics for vital signs and ECG results were calculated by measurement time point for each group. The data were also plotted against time. For continuous variables of hematology tests, blood chemistry tests and urinalysis, summary statistics were calculated by measurement time point for each group. The data were subsequently classified into 3 categories according to the reference ranges. The categorical variables were summarized using the frequencies of subjects in respective categories by measurement time point for each group. For qualitative urinalysis data, category variables were summarized using the frequencies of subjects in respective categories by measurement time point for each group.

Summary of Results

Pharmacokinetics

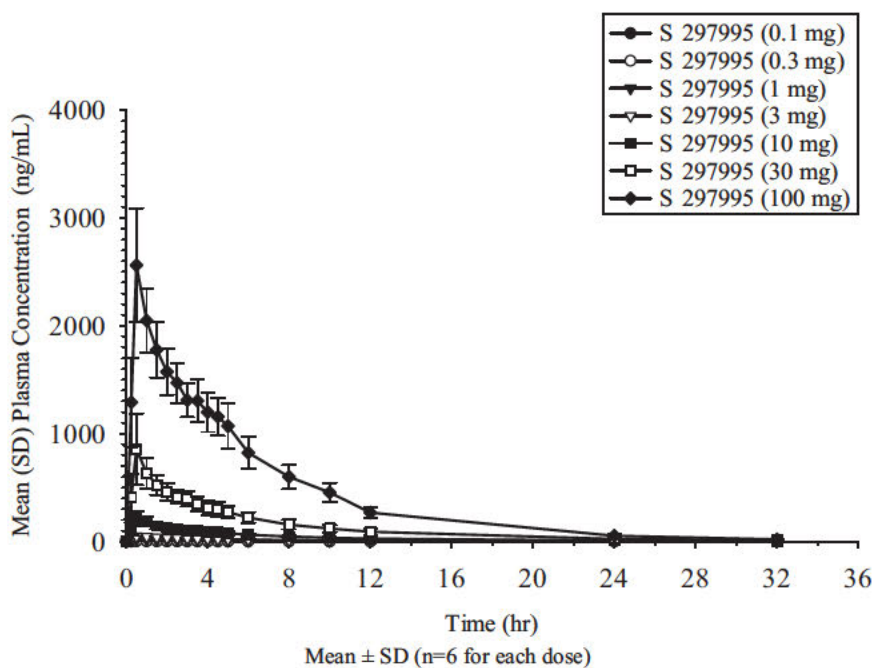
S-297995 was administered orally to healthy adult male subjects in the fasted state as a single dose of 0.1 to 100 mg. The geometric mean C_{max} , AUC_{0-last} and AUC_{inf} were 1.98 to 2510 ng/mL, 10.99 to 13270 ng·hr/mL and 11.60 to 13410 ng·hr/mL, respectively. The C_{max} , AUC_{0-last} and AUC_{inf} increased slightly higher than dose proportional manner to the dose of S-297995 within the range from 0.1 to 100 mg. From the clinical viewpoint, however, the increases in these parameters were considered dose-proportional within the range of 0.1 to 100 mg. The median T_{max} was 0.50 hours, which was almost equivalent among the doses. The geometric mean $t_{1/2,z}$ and CL/F were 5.15 to 9.24 hours and 7.46 to

9.35 L/hr, respectively, within the range from 0.1 to 100 mg.

The ratio of the AUC_{inf} of Nor-S-297995, the primary metabolite of S-297995, to that of unchanged S-297995 ($Ratio_{AUC}$) was 0.201 to 0.286 within the range of 0.1 to 100 mg. The geometric mean $t_{1/2,z}$ of Nor-S-297995 was longer than that of unchanged S-297995; 11 to 27 hours within the range of 0.1 to 100 mg. The geometric means of the $Ratio_{AUC}$ of S-297995 3-*O*- β -D-glucuronide and S-297995 6-*O*- β -D-glucuronide, the other metabolites, were 3% or less and 1% or less, respectively. The AUC_{inf} of Benzamidine was below the lower limit of quantification (0.3 ng/mL) at almost all the points within the range of 0.1 to 100 mg.

The geometric means of the urinary excretion rate of unchanged S-297995 were 15.9% to 23.1% within the range of 0.1 to 100 mg and those of Benzamidine were 7.37% to 12.7% within the range of 0.3 to 100 mg. Those of Nor-S-297995, S-297995 3-*O*- β -D-glucuronide and S-297995 6-*O*- β -D-glucuronide were 1% or less.

The results showed the dose-dependency of the C_{max} and AUC of unchanged S-297995 within the dose range of 0.1 to 100 mg.



Plasma concentration – time curve of unchanged S-297995 after single oral administration

Summary of PK parameters of unchanged S-297995 after single oral administration
in the fasted state

Dose group	N	C _{max} ^{a)} (ng/mL)	T _{max} ^{b)} (hr)	AUC _{0-last} ^{a)} (ng·hr/mL)	AUC _{inf} ^{a)} (ng·hr/mL)	t _{1/2,z} ^{a)} (hr)	CL/F ^{a)} (L/hr)	U _r ^{a)} (%)
0.1 mg	6	1.98 (30.9)	0.50 (0.50, 1.0)	10.99 (24.6)	11.60 (25.4)	8.30 (9.8)	8.62 (25.4)	15.9 (29.2)
0.3 mg	6	4.47 (19.3)	0.50 (0.25, 0.50)	29.68 (13.0)	32.53 (16.5)	9.24 (20.4)	9.22 (16.5)	17.8 (10.7)
1 mg	6	16.2 (23.0)	0.50 (0.50, 1.0)	102.9 (8.0)	107.7 (7.9)	7.56 (10.9)	9.28 (7.9)	18.3 (24.2)
3 mg	6	52.2 (14.3)	0.50 (0.25, 1.5)	303.2 (16.0)	320.8 (15.3)	8.13 (14.6)	9.35 (15.3)	23.1 (8.9)
10 mg	6	217 (26.3)	0.50 (0.50, 1.0)	1104 (17.7)	1135 (17.9)	6.62 (6.8)	8.81 (17.9)	20.3 (15.9)
30 mg	6	822 (39.8)	0.50 (0.50, 1.0)	3887 (24.3)	3969 (24.6)	6.10 (5.2)	7.56 (24.6)	18.9 (40.3)
100 mg	6	2510 (23.7)	0.50 (0.50, 0.50)	13270 (16.0)	13410 (16.0)	5.15 (3.9)	7.46 (16.0)	20.5 (21.8)

a) Geometric Mean (CV% of Geometric Mean), b) Median (Min, Max)

Safety

No deaths, serious AEs or AEs leading to withdrawal were reported in the study.

Nine AEs were reported in 9 of the 42 subjects (21.4%) in the S-297995 groups and 3 AEs in 2 of the 14 subjects (14.3%) in the placebo group. Two AEs were reported in 2 of the 6 subjects (33.3%) each at 0.1, 3, 10 and 100 mg. In the 30-mg group, 1 AE were reported in 1 of the 6 subjects (16.7%). The incidence of AEs did not increase as the dose increased.

The AEs in the S-297995 groups included 4 events of diarrhoea (1 each in the 0.1-, 10-, 30- and 100-mg group), 2 events of abdominal pain (1 each in the 10- and 100-mg group), 1 event of abdominal discomfort (in the 0.1-mg group), 1 event of nasopharyngitis (in the 3-mg group) and 1 event of blood creatine phosphokinase increased (in the 3-mg group). For all of these AEs, except for blood creatine phosphokinase increased and nasopharyngitis, a causal relationship with the study drug was not ruled out. These AEs were however mild and recovered without medical treatment. The AEs reported in the placebo group were orthostatic hypotension, dysphoria and blood potassium decreased (1 event each).

Seven AEs, of which a causal relationship with the study drug was not ruled out (ie, ADRs), in 7 of 42 subjects (16.7%) were reported in the S-297995 groups and 2 ADRs in 1 of 14 subjects (7.1%) in the placebo group. The ADRs in the S-297995 groups included 4 events of diarrhoea (1 each in the 0.1-, 10-, 30-, and 100 mg-group), 2 events of abdominal

pain (1 each in the 10- and 100-mg group) and 1 event of abdominal discomfort (in the 0.1-mg group).

Although diarrhoea, abdominal pain and abdominal discomfort were possibly caused by the pharmacological actions of S-297995, however, the incidences or severity of these events did not increase as the dose of S-297995 increased. Neither abnormal vital signs or abnormal ECG findings were reported at any of the doses of S-297995.

The results showed that single oral dose of S-297995 solution/suspension was safe and well tolerated within the dose range of 0.1 to 100 mg.

Adverse events

Dose group	S 297995								Placebo
	0.1 mg	0.3 mg	1 mg	3 mg	10 mg	30 mg	100 mg	Total	
Safety analysis set	6	6	6	6	6	6	6	42	14
Subjects with any AE	2	0	0	2	2	1	2	9	2
Number of AEs	2	0	0	2	2	1	2	9	3
Incidence (%)	33.3	0	0	33.3	33.3	16.7	33.3	21.4	14.3
AE (PT)									
Gastrointestinal disorders									
Diarrhoea	1	0	0	0	1	1	1	4	0
Abdominal pain	0	0	0	0	1	0	1	2	0
Abdominal discomfort	1	0	0	0	0	0	0	1	0
Infections and infestations									
Nasopharyngitis	0	0	0	1	0	0	0	1	0
Investigations									
Blood creatine phosphokinase increased	0	0	0	1	0	0	0	1	0
Blood potassium decreased	0	0	0	0	0	0	0	0	1
Psychiatric disorders									
Dysphoria	0	0	0	0	0	0	0	0	1
Vascular disorders									
Orthostatic hypotension	0	0	0	0	0	0	0	0	1

This table shows the number of subjects with each AE term.

CONCLUSIONS

A single dose of 0.1, 0.3, 1, 3, 10, 30, or 100 mg solution/suspension of S-297995 was administered orally in the fasted state. The peak (C_{max}) and exposure (AUC) of unchanged S-297995 were considered to increase in a dose-proportional manner. The major metabolite of S-297995 was Nor-S-297995, and its Ratio_{AUC} was 0.201 to 0.286 within the range of 0.1 to 100 mg. S-297995 was safe and well tolerated over single doses of 0.1 to 100 mg.

Final Report Date: October 27 2009