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 I multiple dose clinical study of S-297995 in healthy Japanese adult males		
Investigator: [redacted]		
Study Center: [redacted]		
Publication (reference): None		
Studied Period: 3 months From August [redacted], 2009 (the first subject dosed the study drug) to October [redacted], 2009 (the last subject completed)		
Phase of Development: Phase 1		
Objectives To evaluate the safety, tolerability, and pharmacokinetics of multiple 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 3 mg, 10 mg , 30 mg of S-297995 or placebo once daily for 10 days. Within each group of 12 subjects, 9 subjects received S-297995 and 3 subjects received matching placebo orally once daily to evaluate the safety and pharmacokinetics of S-297995. The initial dose was 3 mg. The dose was increased up to 30 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. If it is judged that the administration should not proceed from 3 mg (Step 1) to 10 mg (Step 2) or from 10 mg (Step 2) to 30 mg (Step 3), the subject were transferred to an 1 mg, Extra Step (reserve group) in order to check tolerability to the multiple administration of S-297995. 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 in vital signs (blood pressures in the supine/standing position, pulse rate, respiratory rate, and body temperature) and electrogram (ECG) between before and after dosing

(4) Pharmacokinetic parameters

Study Schedule

	At screening	Hospitalization period												
		The day before administration	Multiple administration (for 10 days)								Posttreatment assessment			
Day	to -2	0	1	2, 3	4	5, 6	7	8	9	10	11	12	13-16	17
Explanation/ informed consent	X													
Background factors	X	X												
Checking for inclusion/exclusion criteria	X	X												
Study drug administration			X	X	X	X	X	X	X	X				
Symptoms and signs	X	X	X[a]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[a]	X	X	X	X
Adverse events			◄											►
Immunological tests	X													
Urine screening tests for drug abuse	X	X												
Vital signs	X[c]	X[c]	X[d]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[d]	X	X	X	X
Hematology tests	X	X	X		X			X			X			X
Blood chemistry tests	X	X	X		X			X			X			X
Blood coagulation tests	X													
Endocrinologic tests	X	X	X[f]	X	X	X	X	X	X	X[f]	X	X	X	X
Urinalysis[g]	X	X	X		X			X			X			X
ECG	X	X	X[h]		X[i]		X[i]			X[h]				X
Blood sampling for measurement of Plasma drug concentration			X[j]	X	X	X	X	X	X	X[j]	X[k]	X[l]	X	X
Urine sampling for measurement of urine drug concentration			◄►							◄►				

X: Conducted (see "25. Details of investigation, observation and examination items and timing")

[a] Observation of symptoms and signs were performed at 0, 1, 4 and 8 hours postdosing on Day 1 and Day 10.
[b] Observation of symptoms and signs were performed at 0 and 4 hours postdosing from Day 2 to Day 9.
[c] Blood pressure in a standing position were also measured.
[d] Checking of vital signs were performed at 0, 1, 4 and 8 hours postdosing on Day 1 and Day 10. (Blood pressure in the standing position were performed only at 0 and 1 hr postdosing)
[e] Checking of vital signs were performed at 0 and 4 hours postdosing from Day 2 to Day 9. (Blood pressure in a standing position need not be measured)
[f] Endocrinological tests were performed at 0, 1, 2, 4 and 8 hours postdosing on Day 1 and Day 10.
[g] Early morning urine were collected.
[h] ECG were performed at 0, 1, 4 and 8 hours postdosing on Day 1 and Day 10.
[i] ECG were performed at 0 and 4 hours postdosing on Day 4 and Day 7.
[j] Blood sampling times for drug concentration measurement: At 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours postdosing on Day 1 and Day 10
[k] Blood sampling times for drug concentration measurement: At 24 and 36 hours postdosing on Day 11
[l] Blood sampling times for drug concentration measurement: At 48 hours postdosing on Day 12

Number of Subjects (Planned and Analyzed)

Target number of subjects: 36

Number of subjects randomized: 36

Number of subjects administered: 27 in the S-297995 group and 9 in the placebo group

Number of subjects in the pharmacokinetic analysis population: 27 (in the S-297995 group)

Number of subjects in the safety analysis population: 36 (n=27 in the S-297995 group and n=9 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 ≥ 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, 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) In a standing position, the systolic blood pressure is decreased by ≥ 20 mm Hg or the diastolic pressure is decreased by ≥ 10 mm Hg, compared to the blood pressure in a supine position, or history of a diagnosis 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 to be 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) Noncompliant with the individual requirements in section "Management of subjects" of the study protocol
(20) Positive results of any of the following tests: serological tests for syphilis, HBs antigen, HCV antibody, or HIV antigen/antibody
(21) Previously received S-297995
(22) Considered inappropriate for the study by the investigator/subinvestigator

Test Product, Dose and Mode of Administration, Lot Number

1. Test Drug (S-297995)

3-mg group and 1-mg group (Extra Step): S-297995 1-mg tablet

10-mg group and 30-mg group: S-297995 10-mg tablet

2. Dosage

3 mg, 10 mg, or 30 mg of S-297995 was administered once daily for 10 days

3. Method of Administration

Subjects received the study drugs in the fasted state in the morning. The study drug were administered orally with 180 mL of Water for Injection (Japanese Pharmacopoeia) once daily.

4. Lot Number (Manufacturing Number)

S-297995 1-mg tablet, [redacted]; S-297995 10-mg tablet; [redacted]

Control Drug, Dose and Mode of Administration, Lot Number

1. Control Drug

Matching placebo tablet of S-297995 1-mg and 10-mg tablets

2. Dosage

Placebo was administered once daily for 10 days, same as in the test drug

3. Method of Administration

Same as in the test drug

4. Lot Number (Manufacturing Number)

S-297995 placebo tablet (PLACEBO-A), [redacted]

Duration of Treatment: 10 days

Criteria for Evaluation

1. Pharmacokinetic Evaluation

The pharmacokinetic parameters (maximum plasma concentration [C_{max}], time to reach C_{max} [T_{max}], area under the plasma concentration-time curve from time 0 to the time at the end of dose interval [τ] [$AUC_{0-\tau}$], elimination half life [$t_{1/2,z}$], mean residence time [MRT_{0-inf}], molar ratio of $AUC_{0-\tau}$ for S-297995 metabolites to $AUC_{0-\tau}$ for unchanged S-297995 [MR_{AUC}], ratio of C_{max} at Day 10 to C_{max} at Day 1 of dosing [R_{Cmax}], and ratio of $AUC_{0-\tau}$ at Day 10 to $AUC_{0-\tau}$ at Day 1 of dosing [R_{AUC}]), and urinary excretion ratio (Ur) of

unchanged S-297995 and its metabolites (Nor-S-297995, S-297995 3-*O*-β-D-glucuronide, S-297995 6-*O*-β-D-glucuronide, S-297995-carboxylic acid, and Benzamidine) were compared between the S-297995 groups.
1) Plasma concentrations of unchanged S-297995 and its metabolites immediately prior to dosing and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours postdosing at Days 1 and 10; prior to dosing at Day 2 to 9; 24, 36, 48, 72, 96, 120, 144, and 168 hours postdosing at Day 11.
2) Urinary concentrations of unchanged S-297995 and its metabolites immediately prior to dosing and 0-12 and 12-24 hours postdosing at Days 1 and 2; 0-12 and 12-24 hours postdosing at Days 10 and 11.

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 sings (supine and standing blood pressures, pulse rate, respiratory rate and body temperature) and ECG were measured to examine changes between 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 to assess the ADRs according to the following criteria (classification of causal relationship and the definitions).

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 classified as 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 the event could not be explained by factors other than the study drug.
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], $AUC_{0-\tau}$ [ng·hr/mL], MRT_{0-inf} [hr], MR_{AUC}, R_{Cmax} and R_{AUC}) and urinary excretion ratio (%) 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 frequencies of adverse events and adverse drug reactions were compiled and the 95% confidence interval of the incidence was calculated using the Clopper-Pearson method. The number of events and incidence of adverse events and adverse drug reactions classified by System Organ Class and by Preferred Term were determined, and the number of subjects, incidence, and number of episodes were calculated for each category of severity, seriousness classification, action taken with the study drug, concomitant or additional treatment, outcome, and causal relationship with the study drug. Laboratory test, examination of vital signs, and ECG tests were performed over time, and the descriptive statistics and frequencies of abnormal values were calculated for each of the measured values. For urinalysis (qualitative), the frequencies of abnormal values were calculated.

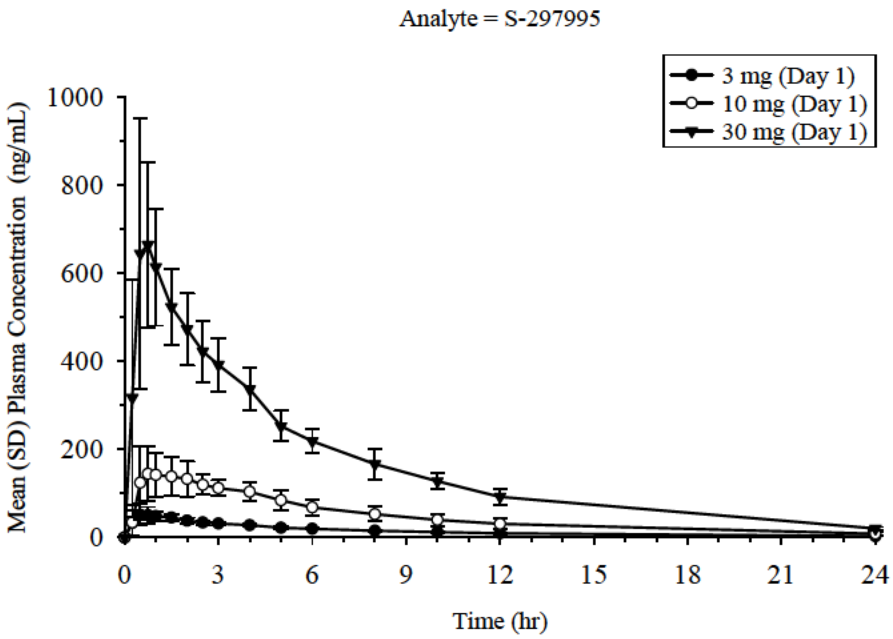
Summary of Results

Pharmacokinetics

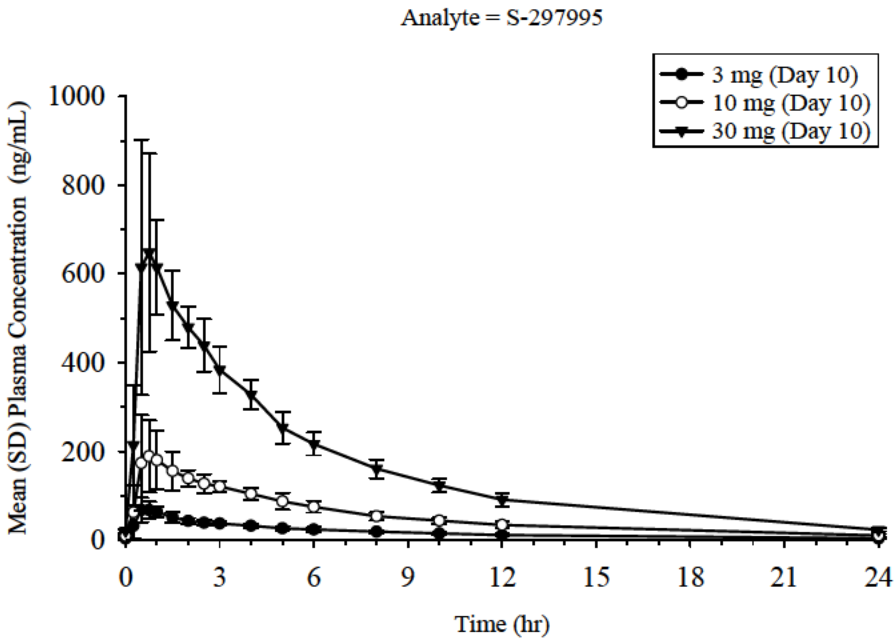
S-297995 was repeatedly administered orally to healthy adult male subjects once daily for 10 days at the doses of 3, 10 and 30 mg.

- Unchanged S-297995 -

The geometric means of C_{max} and $AUC_{0-\tau}$ at the doses of 3, 10, and 30 mg of S-297995 were 56.8, 177 and 727 ng/mL, and 343.7, 1094 and 3764 ng·hr/mL, respectively, on Day 1 and 73.8, 213 and 700 ng/mL, and 407.5, 1230 and 3744 ng·hr/mL, respectively, on Day 10. The plasma concentration reached a steady state within 2 days. The accumulation ratio of C_{max} and $AUC_{0-\tau}$ increased by 0% to 30% and 0% to 20% after repeated administration, respectively. The C_{max} and $AUC_{0-\tau}$ increased in a dose proportional manner in the dose range from 3 to 30 mg. The median T_{max} in the dose range from 3 to 30 mg was 0.50 and 0.75 hours on Day 1 and Day 10, respectively, in all dose groups. The geometric mean of $t_{1/2,z}$ was 37.8 to 45.7 hours on Day 10 in all dose groups, and the geometric mean of MRT_{0-inf} was 7.09 to 9.29 hours on Day 1 in all dose groups.



Mean plasma concentration profiles of unchanged S-297995 during once-daily 10-day repeated oral administration of S-297995 (Day 1, 0-24 hr)



Mean plasma concentration profiles of unchanged S-297995 during once-daily 10-day repeated oral administration of S-297995 (Day 10, 0-24 hr)

PK parameters of unchanged S-297995 during once-daily 10-day repeated oral administration of S-297995

Dose group	Day	N	C_{max} [a] (ng/mL)	T_{max} [b] (hr)	$AUC_{0-\tau}$ [a] (ng·hr/mL)	$t_{1/2,z}$ [a] (hr)	MRT_{0-inf} [a] (hr)	R_{Cmax} [a]	R_{AUC} [a]	Ur (%) [a]
3 mg	1	9	56.8 (29.3)	0.75 (0.25, 1.5)	343.7 (13.5)	-	9.29 (13.9)	-	-	17.6 (19.9)
	10	9	73.8 (27.1)	0.50 (0.50, 1.0)	407.5 (16.8)	37.8 (27.8)	-	1.299 (19.2)	1.186 (11.8)	19.7 (19.2)
10 mg	1	9	177 (24.6)	0.75 (0.50, 4.0)	1094 (21.5)	-	8.09 (19.0)	-	-	15.3 (12.6)
	10	9	213 (30.8)	0.75 (0.50, 5.0)	1230 (14.0)	40.4 (50.5)	-	1.203 (32.1)	1.124 (13.6)	16.5 (10.2)
30 mg	1	9	727 (26.7)	0.75 (0.50, 2.0)	3764 (13.7)	-	7.09 (8.6)	-	-	19.6 (17.0)
	10	9	700 (24.2)	0.75 (0.50, 2.5)	3744 (9.1)	45.7 (18.2)	-	0.963 (24.3)	0.994 (9.0)	19.1 (12.8)

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

- S-297995 metabolites -

The geometric means of the molar ratio of $AUC_{0-\tau}$ for S-297995 metabolites, Nor-S-297995, Benzamidine and S-297995 3-*O*-β-D-glucuronide to that for unchanged S-297995 (MR_{AUC}) were about 20%, 7% and 2%, respectively, on Day 10, except for

Benzamidine after administration of 3 mg. The MR_{AUC} for S-297995 6-*O*-β-D-glucuronide and S-297995-carboxylic acid was less than 1% in all groups. The plasma concentration of Nor-S-297995 reached a steady state within 1 week. The geometric mean of the accumulation ratio of $AUC_{0-\tau}$ (R_{AUC}) for Nor-S-297995 was 1.5 to 1.9 in the dose range from 3 to 30 mg. The median T_{max} for Nor-S-297995 on Day 1 and Day 10 was 3.0 to 4.0 hours in all groups. The geometric mean of $t_{1/2,z}$ for Nor-S-297995 on Day 10 was 62.5 to 79.5 hours at all doses. The plasma concentrations of Benzamidine reached a steady state within 1 week after repeated administration of 10 and 30 mg, but were below the limit of quantification (0.3 ng/mL) at most of measuring points after administration of 3 mg. The geometric means of R_{AUC} for Benzamidine were 4.29 and 3.47, respectively, after repeated administration of 10 and 30 mg. The median T_{max} for Benzamidine on Day 10 of repeated administration of 10 and 30 mg were 12 and 8.0 hours, respectively.

The geometric means of the urinary excretion ratios for unchanged S-297995 were 15.3% to 19.7% in the dose range from 3 to 30 mg on Day 1 and Day 10. The primary metabolite in urine was Benzamidine and its geometric mean of the urinary excretion ratios in the dose range from 3 to 30 mg was 7.77% to 8.71% and 22.1% to 27.6% on Day 1 and Day 10, respectively. The geometric means of the urinary excretion ratios for Nor-S-297995, S-297995 3-*O*-β-D-glucuronide, S-297995 6-*O*-β-D-glucuronide, and S-297995-carboxylic acid were all less than 1%.

The results showed the dose-proportionality of the C_{max} and AUC for unchanged S-297995 in the dose range from 3 to 30 mg.

Safety

S-297995 was repeatedly administered orally to healthy adult male subjects once daily for 10 days at the doses of 3, 10 and 30 mg. Ten AEs were reported in 9 of 27 subjects (33.3%) in the S-297995 groups and 4 AEs in 3 of 9 subjects (33.3%) in the placebo group. Three AEs were reported in 3 of 9 subjects (33.3%) each in the 3- and 10-mg groups. In the 30-mg group, 4 AEs were reported in 3 of 9 subjects (33.3%). The incidence of AEs did not increase as the dose increased. Six ADRs were reported in 5 of 27 subjects (18.5%) in the S-297995 groups, and 1 ADR in 1 of 9 subjects (11.1%) in the placebo group. Two ADRs were reported in 2 of 9 subjects (22.2%) at 3 mg, 1 ADR in 1 of 9 subjects (11.1%) at 10 mg, and 3 ADRs in 2 of 9 subjects (22.2%) at 30 mg.

AEs reported in the S-297995 groups included the following: 4 events of diarrhoea (2 events at 3 mg and 1 event each at 10 and 30 mg), 1 event of abdominal discomfort (30 mg), 3 events of blood triglycerides increased (1 event each at 3, 10 and 30 mg), 1 event of blood creatinine increased (10 mg), and 1 event of blood prolactin increased (30 mg). Among them, all events of diarrhoea, abdominal discomfort, and blood prolactin increased

were considered as ADRs. However, all the AEs reported were mild and recovered without any action taken, including termination of administration and modification of the dose. The incidence of the AEs did not increase or their severity did not worsen as the dose of S-297995 increased.

On the other hand, the AEs reported in the placebo group included the following: 1 event each of abdominal distension, blood creatine phosphokinase increased, C-reactive protein increased, and myoglobin blood increased. Among them, abdominal distension was considered as an ADR. All the AEs reported were mild and recovered without treatment.

No deaths, serious AEs or AEs leading to withdrawal were reported in the study. No other significant AEs were reported. No clinically significant abnormalities were found in vital signs and ECG. The blood prolactin concentrations determined as an endocrinological parameter exhibited diurnal fluctuations in all groups including the placebo group, but no significant difference was found between the placebo group and each of the S-297995 groups.

The results showed that S-297995 orally administered repeatedly once daily for 10 days at the doses of 3, 10 and 30 mg was safe and well tolerated.

Summary of Adverse Events

	S-297995 3 mg N=9	S-297995 10 mg N=9	S-297995 30 mg N=9	Total N=27	Placebo N=9
Adverse Events					
- Number of Subjects	3	3	3	9	3
- Number of Events	3	3	4	10	4
- Percentage of Subjects (%)	33.3	33.3	33.3	33.3	33.3
Gastrointestinal disorders	2 (2)	1 (1)	1 (2)	4 (5)	1 (1)
	22.2%	11.1%	11.1%	14.8%	11.1%
- Diarrhoea	2 (2)	1 (1)	1 (1)	4 (4)	---
	22.2%	11.1%	11.1%	14.8%	---
- Abdominal discomfort	---	---	1 (1)	1 (1)	---
	---	---	11.1%	3.7%	---
- Abdominal distension	---	---	---	---	1 (1)
	---	---	---	---	11.1%
Investigations	1 (1)	2 (2)	2 (2)	5 (5)	2 (3)
	11.1%	22.2%	22.2%	18.5%	22.2%
- Blood triglycerides increased	1 (1)	1 (1)	1 (1)	3 (3)	---
	11.1%	11.1%	11.1%	11.1%	---
- Blood creatine phosphokinase increased	---	---	---	---	1 (1)
	---	---	---	---	11.1%
- Blood creatinine increased	---	1 (1)	---	1 (1)	---
	---	11.1%	---	3.7%	---
- Blood prolactin increased	---	---	1 (1)	1 (1)	---
	---	---	11.1%	3.7%	---
- C-reactive protein increased	---	---	---	---	1 (1)

	---	---	---	---	11.1%
- Myoglobin blood increased	---	---	---	---	1 (1)
	---	---	---	---	11.1%

Note: This table includes the number of subjects (the number of events) and percentage of subjects experiencing AEs. Denominators for the percentages calculation are the numbers of subjects constituting the safety population in each treatment group.

CONCLUSIONS

S-297995 was repeatedly administered orally to healthy adult male subjects once daily for 10 days at the doses of 3, 10 and 30 mg. The plasma concentration of unchanged S-297995 reached a steady state within 2 days. The C_{max} and $AUC_{0-\tau}$ for unchanged S-297995 increased in a dose-proportional manner in the dose range from 3 to 30 mg. The accumulation ratio of C_{max} and $AUC_{0-\tau}$ for unchanged S-297995 increased by 0% to 30% and 0% to 20% after repeated administration, respectively.

On the other hand, all the AEs reported were mild and recovered without treatment and no clinically significant abnormalities were found in vital signs and ECG.. The results showed that S-297995 administration was safe and well tolerated. The blood prolactin concentrations determined as an endocrinological parameter exhibited diurnal fluctuations in all groups including the placebo group, but no significant difference was found between the placebo group and each of the S-297995 groups.

Final Report Date: April 28, 2010