2. SYNOPSIS

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Study Title: A phase 1, randomized, double-blind, single-center, placebo-controlled, ascending single and multiple dose study of S-649266 in healthy adult subjects

Investigator and Study Center:
[redacted]

Publication (reference): None

Studied Period:

Part 1 (Single Dose); March [redacted] 2012 (first subject administered) to May [redacted] 2012 (last subject completed)

Part 2 (Multiple Dose); July [redacted] 2012 (first subject administered) to November [redacted] 2012 (last subject completed)

Study Phase: Phase 1

Objectives:

The primary objectives of the study were:
To evaluate the safety and tolerability of single and multiple doses of S-649266 in healthy adult subjects including non-Japanese.
To determine the pharmacokinetics (PK) of S-649266 in healthy adult subjects including non-Japanese.

The secondary objective of the study was:
To evaluate the production of any S-649266 metabolites and any need to perform a more detailed analysis of any metabolites.

Methodology:

This was a Phase 1, single center, randomized, double-blind, placebo-controlled study in healthy male and female subjects including non-Japanese.

(1) Part 1 (Single Dose)

There were 5 groups (Group A to E), and 3 groups (Group C to E) including both male and female subjects. Subjects in each group were randomized to receive ascending single doses of either S-649266 (6 subjects) or placebo (2 subjects).

The dosage regimens were sequential; safety and PK were evaluated in each cohort before enrolling in the next group. Eligible subjects were admitted to the study center on the day prior to administration and were confined in the study center until the Day 3. Subjects were required to return to the study center on Days 4, 5, and 8±1 for follow-up

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visits.

(2) Part 2 (Multiple Dose)

There were 3 groups including non-Japanese subjects. Subjects in each group were randomized to receive ascending multiple doses of either S-649266 (8 subjects in Groups G and G-2nd and up to 10 subjects in Group H) or placebo (2 subjects).

The dosage regimens of Groups G and H were sequential; safety and PK were evaluated in Group G before enrolling in Group H. The same dosage studied in Group G was repeated in Group G-2nd by using another lot of study drug (Lot number, [redacted]). Eligible subjects were admitted to the study center on the day prior to administration and were confined in the study center until the Day 12. Subjects were required to return to the study center on Days 13, 14 and 17±1 for follow-up visits.

Number of Subjects (Planned and Analyzed):

(1) Part 1 (Single Dose):

We planned up to 48 healthy Japanese adults (36 S-649266, 12 placebo) in 6 groups (Group A to F).

However, Group F (4000 mg) was not conducted according to the rule on the protocol that dose escalation would not proceeded if the predicted C_{max} exceeds a 10-fold lower exposure than the rat NOAEL (C_0 = 1660 μg/mL).

A total of 40 subjects (30 S-649266, 10 placebo) were randomized and analyzed for the pharmacokinetics and safety.

(2) Part 2 (Multiple Dose):

We planned up to 20 healthy male adults (16 S-649266, 4 placebo) in 2 groups (Groups G and H) at the start of this study. We also planned to add two subjects to Group H, if two or more subjects were withdrawn from Group G for reasons other than AEs.

However, the study drug (Lot number, [redacted]) was found to be contaminated with 0.36% iodide ion at the start of Part 2. Mild rashes were observed in 5 of the 8 subjects (62.5%) in the first multiple dose group, Group G (1000 mg every 8 hours [q8h]). As rash is a known side effect of both iodide and cephalosporins [1], administration of 1000 mg q8h was repeated to eliminate the contribution of iodide to the observed frequency of rash. Therefore, Group G-2nd (1000 mg q8h) as the iodide-free study drug (Lot number, [redacted]) was added to Part 2.

A total of 30 subjects (24 S-649266, 6 placebo) were randomized and analyzed for the pharmacokinetics and safety, as two or more subjects were not withdrawn from Group G for reasons other than AEs.

Diagnosis and Main Criteria for Inclusion:

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Healthy adult subjects who satisfied the inclusion/exclusion criteria.

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

Test Product: The study drug for injection was supplied in vials containing 500 mg of S-649266

Dose and Mode of Administration:

(1) Part 1 (Single Dose)

S-649266 was administered by intravenous infusion over 60 minutes at a dose of 100, 250, 500, 1000, or 2000 mg.

(2) Part 2 (Multiple Dose)

S-649266 was administered by intravenous infusion over 60 minutes at 8-hour interval for 10 days (ie, single dose on the morning of Days 1 and 10, and three times a day from Day 2 to 9, 26 times in total) at a dose of 1000 or 2000 mg.

Lot Number:

[redacted] (contaminated with 0.36% iodide ion); Group A to E in Part 1 and Group G in Part 2.

[redacted] (not contaminated with iodide); Groups G-2nd and H in Part 2.

Duration of Treatment: Single dose (1 day) or multiple dose (10 days, 26 times in total).

Reference Therapy:

Dose and Mode of Administration:

Test Product: Isotonic sodium chloride solution, the Japanese Pharmacopeia (JP) (Otsuka Normal Saline)

Dose and Mode of Administration:

(1) Part 1 (Single Dose)

Matching placebo was administered by intravenous infusion over 60 minutes.

(2) Part 2 (Multiple Dose)

Matching placebo was administered by intravenous infusion over 60 minutes at 8-hour interval for 10 days (ie, single dose on the morning of Days 1 and 10, and three times a day from Day 2 to 9, 26 times in total).

Lot Number: [redacted]

Criteria for Evaluation:

Pharmacokinetic Analysis:

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Blood and urine samples were collected for PK analysis.

Bioanalytic Assessment:

Measurement method: Liquid chromatography/tandem mass spectrometry (LC/MS/MS)

Lower limit of quantification of S-649266 in plasma and urine: 0.1 μg/mL for plasma, 1 μg/mL for urine

Pharmacokinetic Parameters:

The estimated pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-8}}$, $AUC_{0\text{-}\tau}$, λ_z, $t_{1/2,z}$, CL, MRT, Feu, and CL_R) were summarized using descriptive statistics, including the mean, SD, CV%, median, min, max, geometric mean, and CV% for geometric mean (CV% Geometric Mean). T_{max} was summarized using descriptive statistics, including mean, SD, CV%, median, min, and max.

C_{max}	Maximum plasma concentration
T_{max}	Time to maximum plasma concentration
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration after dosing
$AUC_{0\text{-inf}}$	Area under the concentration-time curve extrapolated from time zero to infinity
$AUC_{0\text{-8}}$	Area under the concentration-time curve over the dosing interval (8 hours) following the initial dosing
$AUC_{0\text{-}\tau}$	Area under the concentration-time curve over the dosing interval τ (8 hours)
λ_z	Terminal elimination rate constant based on data points in the terminal phase
$t_{1/2,z}$	Terminal elimination half-life
CL	Total clearance
MRT	Mean residence time
Feu	Urinary excretion ratio relative to dose
CL_R	Renal clearance

Safety:

Safety was assessed through serial physical examinations, resting vital signs, 12-lead ECG recordings, continuous ECG recordings and collection of conventional laboratory data (hematology, blood chemistry, and urinalysis). All data collected were assessed for severity, changes from baseline, and their relationship to treatment with study drug. All adverse events reported spontaneously by the subject, or observed by the investigator or

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sub-investigator was recorded.

Statistical Methods:

Pharmacokinetics:

PK parameters of S-649266 were calculated based on the plasma and urine concentrations of S-649266 by applying a model independent approach. Dose proportionality of PK parameters was examined by using a power model. Dose dependency, dose independency, effect of multiple doses, and accumulation ratio of PK parameters were examined with an analysis of variance (ANOVA). Achievement of steady state was assessed by visual inspection of plots and linear regression for plasma trough concentrations.

Safety:

The number of cases of adverse events (AEs) and the number of subjects experiencing any AEs were summarized by each treatment group and the incidence was calculated. The same summarization and calculation were performed for adverse drug reactions (ADRs).

Pharmacokinetic Results:

(1) Part 1 (Single Dose)

Geometric mean values (CV% Geometric Mean) ranged from 7.76 to 156 μg/mL (4.6% to 10.7%) for C_{max}, 17.03 to 388.9 μg·hr/mL (6.3% to 22.5%) for $AUC_{0\text{-last}}$, and 17.49 to 389.7 μg·hr/mL (6.3% to 22.7%) for $AUC_{0\text{-inf}}$. Low to moderate inter-individual variability for the plasma exposure was suggested in all dose groups.

Geometric mean values (CV% Geometric Mean) ranged from 1.98 to 2.74 hours (4.4% to 15.5%) for $t_{1/2,z}$, 4.60 to 5.96 L/hr (6.3% to 22.7%) for CL, 2.18 to 2.51 hours (3.9% to 15.2%) for MRT, 61.5% to 68.4% (3.2% to 16.2%) for $Feu_{0\text{-}48}$, and 3.03 to 4.06 L/hr (8.8% to 38.3%) for CL_R. These parameters were shown to be dose independent.

The estimates of slopes (95% CI) for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of S-649266 were 1.00 (0.965 to 1.04), 1.04 (0.983 to 1.09), and 1.03 (0.975 to 1.08), respectively. These estimates of slopes were close to 1 and the corresponding 95% CI included 1. These indicated dose-proportional increase in C_{max}, $AUC_{0\text{-last,}}$ and $AUC_{0\text{-inf}}$ of S-649266 across the dose range of 100 to 2000 mg.

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Summary of the Pharmacokinetic Parameters of S-649266 Following Single Intravenous Infusion of 100 to 2000 mg

PK parameter	Dose (mg)				
	100 (N=6)	250 (N=6)	500 (N=6)	1000 (N=6)	2000 (N=6)
C_{max} (µg/mL)	7.76 (7.8)	18.9 (4.9)	46.6 (10.7)	76.4 (4.6)	156 (7.9)
T_{max} (hr)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
$AUC_{0\text{-last}}$ (µg·hr/mL)	17.03 (8.5)	41.41 (6.3)	108.0 (22.5)	167.3 (6.9)	388.9 (9.0)
$AUC_{0\text{-inf}}$ (µg·hr/mL)	17.49 (8.5)	41.94 (6.3)	108.6 (22.7)	168.1 (7.0)	389.7 (9.0)
$t_{1/2,z}$ (hr)	2.00 (4.4)	1.98 (5.5)	2.12 (15.5)	2.26 (5.8)	2.74 (10.2)
CL (L/hr)	5.72 (8.5)	5.96 (6.3)	4.60 (22.7)	5.95 (7.0)	5.13 (9.0)
MRT (hr)	2.23 (3.9)	2.18 (6.2)	2.34 (15.2)	2.24 (4.4)	2.51 (4.7)
$Feu_{0\text{-}48}$ (%)	68.4 (3.2)	64.0 (5.4)	65.8 (16.2)	68.3 (6.0)	61.5 (10.6)
CL_R (L/hr)	3.91 (8.8)	3.81 (10.7)	3.03 (38.3)	4.06 (11.2)	3.16 (16.8)

Geometric mean (CV% Geometric Mean) is shown except for T_{max} where median and range (minimum, maximum) are shown.

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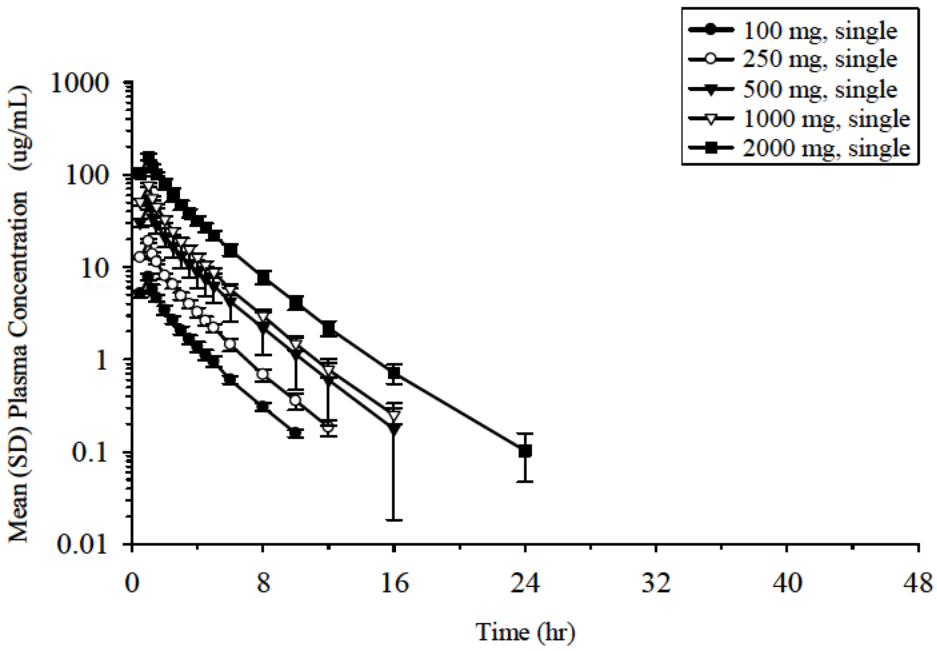
Mean Plasma S-649266 Concentration Profiles Following Single Intravenous Infusion of 100 to 2000 mg (N = 6 per dose)

Analyte = S-649266



Logarithmic y-axis

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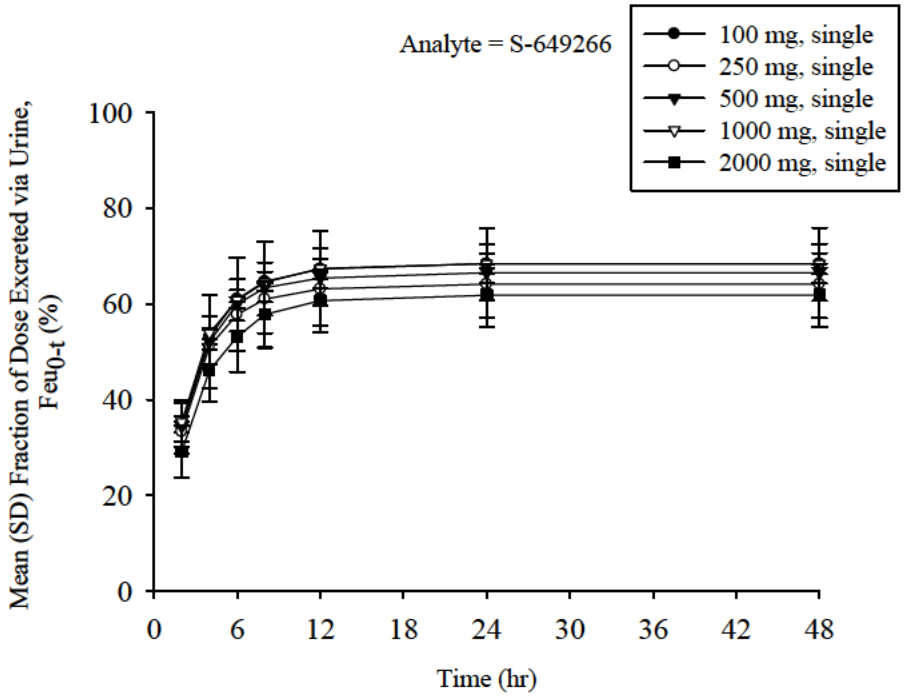
Mean S-649266 Cumulative Fraction of Dose Excreted via Urine Profiles Following Single Intravenous Infusion of 100 to 2000 mg (N = 6 per dose)



(2) Part 2 (Multiple Dose)

Plasma concentration profiles and linear regression for plasma trough concentrations indicated achievement of steady state within 1 day after initiation of multiple dosing (Day 3). Linear regression for plasma trough concentrations also suggested the achievement. Plasma concentrations following 1000 mg dosing were similar between the iodide-contaminated drug and the iodide-free drug. Dose-proportional increase in C_{max} and $AUC_{0-\tau}$ was suggested following multiple dose. Accumulation ratios of C_{max} and AUC by dosing every 8 hours were 1.069 and 1.053 at 1000 mg, and 1.084 and 1.164 at 2000 mg, respectively. The comparisons of AUC (AUC_{0-inf} and $AUC_{0-\tau}$), CL, and CL_R between Days 1 and 10 indicated no change of PK by multiple dose.

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Summary of the Pharmacokinetic Parameters of S-649266 Following Multiple Intravenous Infusion of 1000 and 2000 mg

PK parameter	Dose (mg)					
	1000 (iodide-contaminated)		1000 (iodide-free)		2000 (iodide-free)	
N	8	8	8	7[a]	8	8
Day	1	10	1	10	1	10
C_{max} (μg/mL)	72.2 (12.0)	69.8 (13.3)	68.1 (16.2)	72.2 (11.5)	141 (22.7)	153 (12.9)
T_{max} (hr)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.00 (1.00, 1.00)	1.00 (1.00, 1.25)	1.00 (1.00, 1.25)	1.00 (1.00, 1.25)
AUC_{0-8} (μg·hr/mL)	165.5 (10.7)	NE	160.9 (10.5)	NE	314.8 (14.9)	NE
AUC_{0-last} (μg·hr/mL)	176.4 (11.0)	NE	171.0 (10.6)	NE	337.2 (15.6)	NE
AUC_{0-inf} (μg·hr/mL)	177.4 (10.9)	NE	172.0 (10.6)	NE	338.5 (15.5)	NE
$AUC_{0-\tau}$ (μg·hr/mL)	NE	160.5 (13.5)	NE	168.6 (11.0)	NE	366.5 (14.0)
$t_{1/2,z}$ (hr)	2.37 (11.4)	2.35 (18.5)	2.25 (8.8)	2.19 (4.3)	2.40 (13.2)	2.72 (21.6)
CL (L/hr)	5.64 (10.9)	6.23 (13.5)	5.81 (10.6)	5.93 (11.0)	5.91 (15.5)	5.46 (14.0)
MRT (hr)	2.49 (12.1)	NE	2.50 (6.8)	NE	2.53 (13.5)	NE
Feu[b] (%)	70.9 (6.7)	70.0 (6.1)	63.8 (12.3)	64.7 (12.8)	67.7 (4.7)	71.4 (5.3)
CL_R (L/hr)	4.02 (14.8)	4.36 (12.8)	3.73 (14.9)	3.85 (17.8)	4.02 (17.2)	3.89 (15.1)

Geometric mean (CV% Geometric Mean) is shown except for T_{max} where median and range (minimum, maximum) are shown.
NE, Not evaluated.
a N = 6 for Feu and CL_R.
b Feu_{0-24} for Day 1 and Feu_{0-8} for Day 10.

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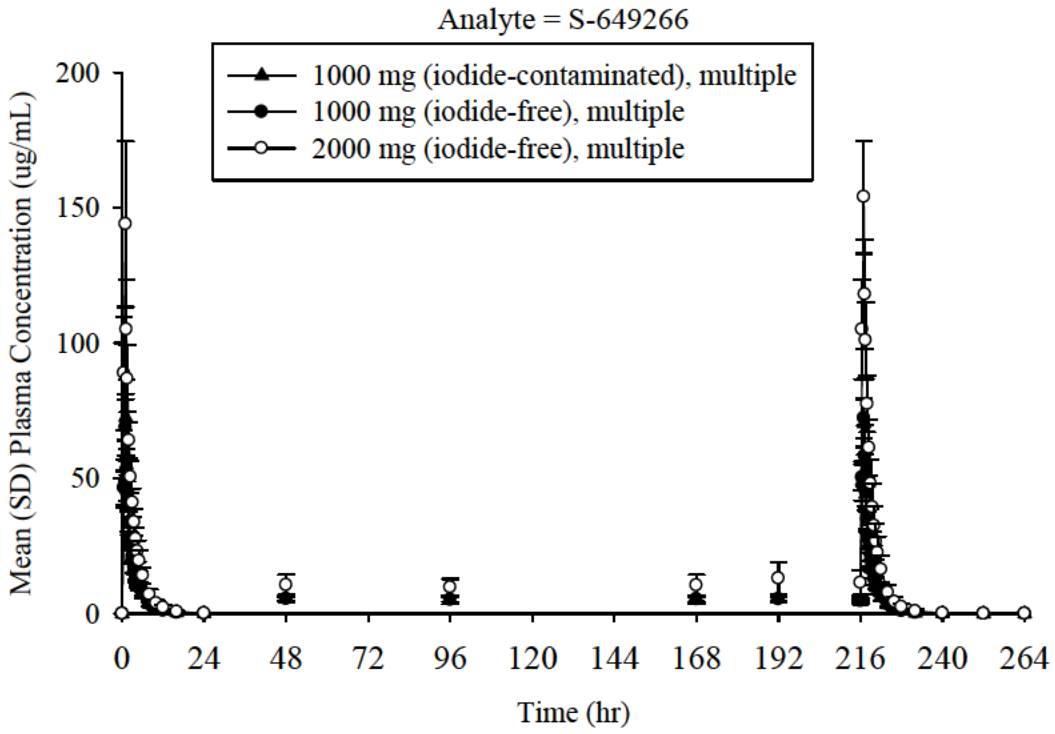
Mean Plasma S-649266 Concentration Profiles Following Multiple Intravenous Infusion of 1000 and 2000 mg (N = 8 per dose)



N = 8 in each dose except for Day 10 for iodide-free drug of 1000 mg (N = 7).

Safety Results:

(1) Part 1 (Single Dose)

- In total, 10 AEs were reported by 6 of the 30 subjects (20.0%) in all S-649266 groups. Of them, 9 AEs reported by 6 subjects were considered possibly, or probably related to the study treatment. These included diarrhoea, rash, abdominal pain, white blood cell count increased, red blood cells urine positive, white blood cells urine positive, and blood urine present.
- In total, 5 AEs were reported by 4 of the 10 subjects (40.0%) in the placebo group. Of them, 4 AEs reported by 3 subjects were considered possibly related to the study treatment. These included diarrhoea, nausea, dizziness, and white blood cells urine.

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Incidence of Each Adverse Event in Part 1 by Cohort

System Organ Class - Preferred Term	S-649266 100 mg N=6	S-649266 250 mg N=6	S-649266 500 mg N=6	S-649266 1000 mg N=6	S-649266 2000 mg N=6	S-649266 Total N=30	Placebo N=10
Subjects with any AEs	1 (1) 16.7%	0	1 (2) 16.7%	2 (4) 33.3%	2 (3) 33.3%	6 (10) 20.0%	4 (5) 40.0%
Gastrointestinal Disorders	0	0	1 (2) 16.7%	0	1 (1) 16.7%	2 (3) 6.7%	2 (2) 20.0%
- Diarrhoea	0	0	1 (1) 16.7%	0	1 (1) 16.7%	2 (2) 6.7%	1 (1) 10.0%
- Abdominal Pain	0	0	1 (1) 16.7%	0	0	1 (1) 3.3%	0
- Nausea	0	0	0	0	0	0	1 (1) 10.0%
Investigations	1 (1) 16.7%	0	0	1 (3) 16.7%	1 (1) 16.7%	3 (5) 10.0%	2 (2) 20.0%
- White Blood Cells Urine Positive	0	0	0	1 (1) 16.7%	0	1 (1) 3.3%	1 (1) 10.0%
- Blood Creatine Phosphokinase Increased	0	0	0	1 (1) 16.7%	0	1 (1) 3.3%	0
- Blood Urine Present	0	0	0	1 (1) 16.7%	0	1 (1) 3.3%	0
- Red Blood Cells Urine Positive	1 (1) 16.7%	0	0	0	0	1 (1) 3.3%	0
- White Blood Cell Count Increased	0	0	0	0	1 (1) 16.7%	1 (1) 3.3%	0
- Blood Glucose Increased	0	0	0	0	0	0	1 (1) 10.0%
Nervous System Disorders	0	0	0	0	0	0	1 (1) 10.0%
- Dizziness	0	0	0	0	0	0	1 (1) 10.0%
Skin And Subcutaneous Tissue Disorders	0	0	0	1 (1) 16.7%	1 (1) 16.7%	2 (2) 6.7%	0
- Rash	0	0	0	1 (1) 16.7%	1 (1) 16.7%	2 (2) 6.7%	0

[Table 12.2.2-1]

- All AEs were mild and resolved. There were no deaths, SAEs or AEs leading to withdrawal.
- There was no dose-response trend in incidence of AEs; the incidence of AEs was relatively evenly spread between the dose groups, including placebo group.
- No abnormal findings were found in 12-lead ECG or a continuous ECG or abnormal changes in vital signs.

(2) Part 2 (Multiple Dose)

- In total, 17 AEs were reported by 7 of the 8 subjects (87.5%) in the 1000-mg group (the iodide-contaminated study drug). Of them, 16 AEs reported by 7 subjects were considered possibly, or probably related to the study treatment. These included rash, blood thyroid stimulating hormone decreased, pyrexia, headache, blood thyroid stimulating hormone increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood urea increased, and blood urine present.

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- In total, 28 AEs were reported by 12 of the 16 subjects (75.0%) in the 1000-mg and 2000-mg groups (the iodide-free study drug). Of them, 22 AEs reported by 12 subjects were considered possibly, or probably related to the study treatment. These included alanine aminotransferase increased, aspartate aminotransferase increased, diarrhoea, pyrexia, rash, white blood cell count increased, abdominal pain, blood creatine phosphokinase increased, white blood cells urine positive, headache, and oropharyngeal pain.

Incidence of Each Adverse Event in Part 2 by Cohort

System Organ Class - Preferred Term	S-649266 1000 mg [a] N=8	S-649266 1000 mg [b] N=8	S-649266 2000 mg [b] N=8	S-649266 Total [b] N=16	Placebo N=6
Subjects with any AEs	7 (17) 87.5%	6 (15) 75.0%	6 (13) 75.0%	12 (28) 75.0%	4 (6) 66.7%
Gastrointestinal Disorders	0	2 (3) 25.0%	1 (1) 12.5%	3 (4) 18.8%	0
- Diarrhoea	0	2 (3) 25.0%	0	2 (3) 12.5%	0
- Abdominal Pain	0	0	1 (1) 12.5%	1 (1) 6.3%	0
General Disorders and Administration Site Conditions	2 (2) 25.0%	1 (1) 12.5%	1 (1) 12.5%	2 (2) 12.5%	0
- Pyrexia	2 (2) 25.0%	1 (1) 12.5%	1 (1) 12.5%	2 (2) 12.5%	0
Infections and Infestations	0	1 (1) 12.5%	0	1 (1) 6.3%	0
- Upper Respiratory Tract Infection	0	1 (1) 12.5%	0	1 (1) 6.3%	0
Investigations	5 (9) 62.5%	4 (9) 50.0%	4 (7) 50.0%	8 (16) 50.0%	4 (6) 66.7%
- Alanine Aminotransferase Increased	1 (1) 12.5%	3 (3) 37.5%	1 (1) 12.5%	4 (4) 25.0%	3 (3) 50.0%
- Aspartate Aminotransferase Increased	1 (1) 12.5%	3 (3) 37.5%	1 (1) 12.5%	4 (4) 25.0%	1 (1) 16.7%
- Blood Creatine Phosphokinase Increased	0	1 (2) 12.5%	2 (2) 25.0%	3 (4) 18.8%	1 (1) 16.7%
- White Blood Cell Count Increased	0	0	2 (2) 25.0%	2 (2) 12.5%	0
- Blood Thyroid Stimulating Hormone Increased	3 (3) 37.5%	0	0	0	0
- Blood Lactate Dehydrogenase Increased	0	1 (1) 12.5%	0	1 (1) 6.3%	0
- Blood Urea Increased	1 (1) 12.5%	0	0	0	1 (1) 16.7%
- White Blood Cells Urine Positive	0	0	1 (1) 12.5%	1 (1) 6.3%	0
- Blood Thyroid Stimulating Hormone Decreased	1 (2) 12.5%	0	0	0	0
- Blood Urine Present	1 (1) 12.5%	0	0	0	0
Nervous System Disorders	1 (1) 12.5%	0	1 (1) 12.5%	1 (1) 6.3%	0
- Headache	1 (1) 12.5%	0	1 (1) 12.5%	1 (1) 6.3%	0
Respiratory, Thoracic and Mediastinal Disorders	0	1 (1) 12.5%	0	1 (1) 6.3%	0
- Oropharyngeal Pain	0	1 (1) 12.5%	0	1 (1) 6.3%	0
Skin and Subcutaneous Tissue Disorders	5 (5) 62.5%	0	2 (3) 25.0%	2 (3) 12.5%	0
- Rash	5 (5) 62.5%	0	2 (3) 25.0%	2 (3) 12.5%	0

[Table 12.2.2-2]

[a] The study drug (S-649266) was contaminated with iodide (Lot number, [redacted]).

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- One AE (pyrexia) was moderate; the other AEs were mild in severity. All AEs were resolved or resolving. There were no deaths or SAEs. One subject was withdrawn from the study drug due to an AE.
- There was no dose-response trend in incidence of AEs; the incidence of AEs was relatively evenly spread between the dose groups, including placebo group.
- No abnormal findings were found in 12-lead ECG or a continuous ECG. No abnormal changes in vital signs were found, except for the subjects with pyrexia.

CONCLUSIONS

Pharmacokinetics:

The following results were obtained based on the pharmacokinetic analyses for the plasma concentration data and urine excretion data following single (100 to 2000 mg) and multiple (1000 and 2000 mg) intravenous infusion over 60 minutes:

Single dose

- Dose-proportional increase in C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of S-649266 was shown across the dose range of 100 to 2000 mg.
- Dose independency of $t_{1/2,z}$, CL, MRT, $Feu_{0\text{-}48}$, and CL_R of S-649266 was shown across the dose range of 100 to 2000 mg.
- Geometric mean $t_{1/2,z}$ of S-649266 ranged from 1.98 to 2.74 hours.
- Geometric mean $Feu_{0\text{-}48}$ of S-649266 ranged from 61.5% to 68.4%.
- PK parameters exhibited low to moderate inter-individual variability in all dose groups.

Multiple dose

- Dose-proportional increase in C_{max} and AUC was suggested following multiple dose.
- Plasma concentration reached steady state within 1 day after initiation of multiple dose.
- Accumulation ratios of C_{max} and AUC by dosing every 8 hours were 1.069 and 1.053 at 1000 mg, and 1.084 and 1.164 at 2000 mg, respectively.
- PK was not changed by multiple dose.

Safety:

The study indicates that single and multiple intravenous dose of S-649266 up to 2000 mg was well-tolerated in healthy subjects.

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