2. SYNOPSIS

Sponsor: Shionogi & Co., Ltd.	**Individual Study Table Referring to Part of the Dossier**	**(*For National Authority Use only*)**
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Study Title: A Phase 1, Single-Center, Open-Label, Intrapulmonary Pharmacokinetics Study after Single Dose of S-649266 in Healthy Adult Subjects

Investigator and Study Center:
[redacted]

Publication (reference): None

Studied Period:
April [redacted] 2013 (first subject administered) to June [redacted] 2013 (last subject completed)

Study Phase: Phase 1

Objectives:

The primary objective of the study was:

To determine the intrapulmonary pharmacokinetics after a single dose of S-649266 in healthy adult male subjects.

The secondary objective of the study was:
To evaluate the safety after single dose of S-649266 in healthy adult male subjects.

Methodology:

The study was a phase 1, single-center, open-label study in healthy adult male subjects.

Each subject underwent one bronchoscopy with bronchoalveolar lavage (BAL) to collect BAL fluid (BALF) and blood was collected prior to the beginning of the bronchoscopy for measurements of urea and red blood cell (RBC) counts. Fifteen subjects were assigned to one of the three BAL collection time-points: at 1, 2, or 4 hours from the start of the infusion [0 (just after the completion of the infusion), 1, or 3 hours after the completion of the infusion]. The time-point assigned for each subject was determined by the investigator based on the bronchoscopy schedule. After the study started, it turned out that the BALF concentrations of S-649266 were predicted to be measurable at 6 hours from the start of the infusion based on the concentration data available between 1 and 4 hours from the start of the infusion. Taking this into consideration, the BAL collection at 6 hours was added and 5 subjects were assigned to the additional BAL collection time-point.

The study consisted of screening (Day −28 to −3), admission to the study center (Day −1), administration of study drug (Day 1), discharge from the study center (Day 3), and outpatient visits (Days 4, 5, and 8±1).

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Number of Subjects (Planned and Analyzed):

Planned: 15 or up to 20 subjects

Enrolled: 20 subjects

Analyzed: 20 (pharmacokinetics); 20 (safety)

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were healthy male volunteers aged 20 to 40 years inclusive, with body weight of ≥ 50.0 and ≤ 80.0 kg and a body mass index (BMI) of ≥ 18.5 and < 25.0 kg/m^2 who were able to understand the study and comply with all study procedures, and willing to provide written informed consent prior to screening.

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:

S-649266 was administered by a single intravenous infusion over 60 minutes at a dose of 2000 mg.

Lot Number: [redacted]

Duration of Treatment: Single dose.

Reference Therapy:

None.

Criteria for Evaluation:

Pharmacokinetic Analyses:

Blood and BALF samples were collected for pharmacokinetic analyses.

Bioanalytical Assessment:

Analytical method: Liquid chromatography/tandem-mass spectrometry (LC/MS/MS).

Lower limit of quantification for S-649266 in plasma, BALF, and cell suspension: 0.1 μg/mL for plasma, 0.005 μg/mL for BALF, and 0.005 μg/mL for cell suspension.

Pharmacokinetic Parameters:

$R_{C,E/P}$ and $R_{C,A/P}$ were summarized using descriptive statistics, including the mean, SD, CV%, median, min, max, geometric mean, and CV% for geometric mean (CV% Geometric Mean). The plasma pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{- inf}}$, $AUC_{0\text{-t}}$, λ_z, $t_{1/2,z}$, CL, and MRT) were summarized using descriptive statistics, including the mean, SD, CV%, median, min, max, geometric mean, and CV% Geometric Mean. The T_{max} was summarized using descriptive statistics, including mean, SD, CV%, median, min, and max. The epithelial lining fluid (ELF) and alveolar macrophage (AM)

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pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, λ_z, $t_{1/2,z}$, $R_{AUC,E/P}$, and $R_{AUC,A/P}$) were estimated.

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
$AUC_{0\text{-}t}$	Area under the concentration-time curve over the last nominal sampling time (i.e. 6 hours) for the mean ELF and AM concentration
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
$R_{C,E/P}$	Concentration ratio in ELF to plasma at corresponding time
$R_{C,A/P}$	Concentration ratio in AM to plasma at corresponding time
$R_{AUC,E/P}$	AUC ratio in ELF to plasma
$R_{AUC,A/P}$	AUC ratio in AM to plasma

Safety:

Safety was assessed through serial physical examinations, resting vital signs, 12-lead 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 with the study drug. All adverse events (AEs) reported spontaneously by the subject, or observed by the investigator or subinvestigator were recorded.

Statistical Methods:

Pharmacokinetics:

Pharmacokinetic parameters of S-649266 were calculated based on the concentrations in plasma, ELF, and AM according to the model independent approach.

Safety:

The number of AEs and the number of subjects experiencing any AEs were summarized and the incidence was calculated. Similar procedures were performed for adverse drug reactions (ADRs).

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Pharmacokinetic Results:

The ELF S-649266 concentration profile appeared to be parallel to the plasma concentration profile. The geometric mean concentration ratios of ELF to plasma over 6 hours ranged from 0.0927 to 0.116. The geometric mean AM S-649266 concentrations over 6 hours ranged from 0.713 to 1.23 μg/mL and the geometric mean concentration ratios of AM to plasma over 6 hours ranged from 0.00496 to 0.104. The AUC ratios of ELF to plasma and AM to plasma were 0.101 and 0.0177, respectively.

Summary of ELF and AM S-649266 Concentrations and Concentration Ratios in ELF to Plasma and AM to Plasma Following Single Intravenous Infusion of 2000 mg of S-649266

Time (hr)	C_{ELF} (μg/mL)	$R_{C,E/P}$	C_{AM} (μg/mL)	$R_{C,A/P}$
1	13.8 (26.9)	0.0955 (31.9)	0.713 (65.7)[a]	0.00496 (74.0)[a]
2	6.69 (23.1)	0.0927 (33.4)	0.940 (36.4)[a]	0.0133 (46.8)[a]
4	2.78 (37.2)	0.0936 (46.1)	0.925 (72.8)[a]	0.0314 (58.7)[a]
6	1.38 (11.8)	0.116 (13.2)	1.23 (19.2)	0.104 (36.7)

N = 5. a: N = 4. Geometric mean (CV% Geometric Mean).
C_{ELF} and C_{AM} are the S-649266 concentration in the ELF and the AM, respectively.
$R_{C,E/P}$ and $R_{C,A/P}$ are the concentration ratios of ELF to plasma and AM to plasma, respectively.

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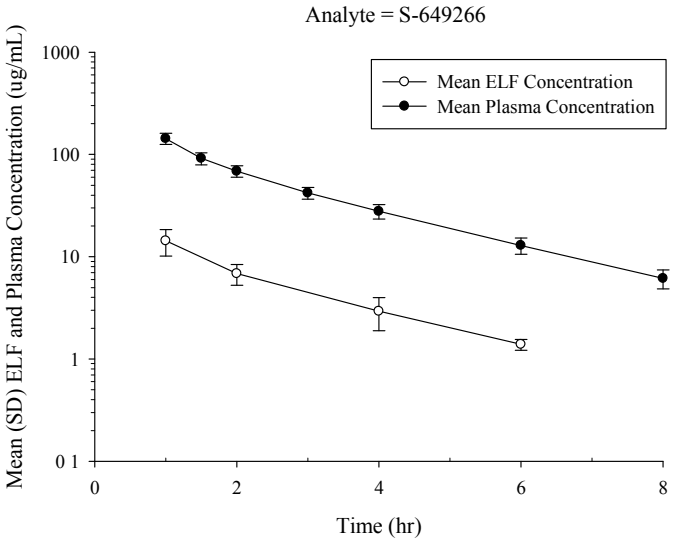
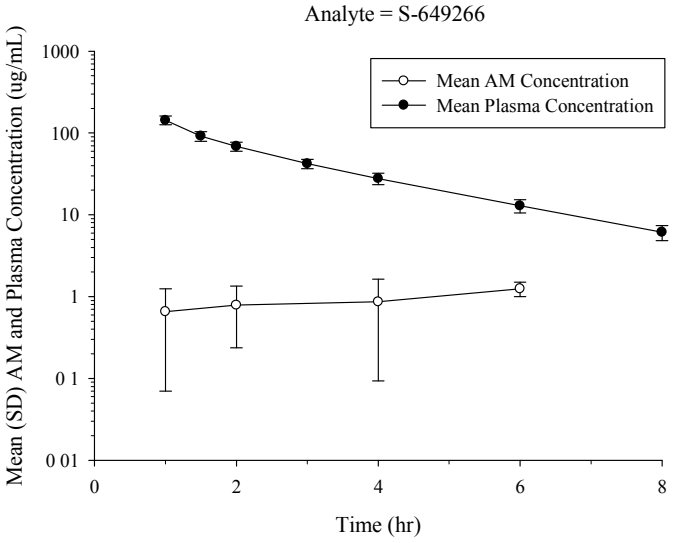
Mean Plasma and ELF S-649266 Concentration Profiles Following Single Intravenous Infusion of 2000 mg of S-649266



N = 20 at each time point for plasma. N = 5 at each time point for ELF. Logarithmic y-axis.

Mean Plasma and AM S-649266 Concentration Profiles Following Single Intravenous Infusion of 2000 mg of S-649266



N = 20 at each time point for plasma. N = 5 at each time point for AM. Logarithmic y-axis.

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Safety Results:

- In total, 27 AEs were reported in 14 of the 20 subjects (70.0%). Of the AEs reported, most were not considered drug-related, except one AE (vomiting). All the AEs were mild in severity, except for one moderate AE (respiratory tract infection). All the AEs resolved by the end of the study.
- There were no deaths, SAEs or AEs leading to early withdrawal from the study.
- The mean value of CRP was slightly above ULN on Days 2 and 3. Although 12 subjects experienced AEs of CRP increased, all the AEs of CRP increased were judged to be due to BAL procedure and considered not related to the study drug.
- No significant changes in vital signs were observed with the exception of 2 AEs relating to increased body temperature. Neither of them was considered drug-related.
- No abnormal findings were reported on the 12-lead ECG recordings.

CONCLUSIONS

Pharmacokinetics:

The following results were obtained based on the pharmacokinetic analyses for the S-649266 concentration data in plasma, ELF and AM following a single intravenous infusion of 2000 mg of S-649266 over 60 minutes:

- The ELF concentration profile appeared to be parallel to the plasma concentration profile.
- The geometric mean ELF concentrations were 13.8, 6.69, 2.78, and 1.38 μg/mL at 1, 2, 4, and 6 hours from the start of the infusion, respectively. The geometric mean concentration ratios of ELF to plasma over 6 hours ranged from 0.0927 to 0.116.
- The geometric mean AM concentrations over 6 hours ranged from 0.713 to 1.23 μg/mL.
- The AUC ratios of ELF and AM to plasma were 0.101 and 0.0177, respectively.

Safety:

No safety signals were identified following a single intravenous infusion of 2000 mg of S-649266 to healthy subjects in this study.

Final Report Date: October 22, 2013