2. SYNOPSIS

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	**(*For National Authority Use only*)**
Name of Finished Product: [^{14}C]-S-649266	**Volume:**	
Name of Active Ingredient: S-649266	**Page:**	
Study Title: A Study to Characterize Metabolism, Excretion, and Mass Balance of S-649266 after Intravenous Administration of a 1000 mg (100 µCi) Dose of [^{14}C]-S-649266 in Healthy Adult Male Subjects		
Principal Investigator and Study Center: [redacted]		
Publication (reference): None		
Studied Period: [redacted] Nov 2015 (first subject dosed) to Nov 2015 (last subject completed)		
Study Phase: Phase 1		
Objectives: Primary objectives: • To investigate the route(s) of elimination and mass balance of S-649266 after intravenous administration of a single 1000 mg (approximately equivalent to [~] 100 microcurie [µCi] = 3.7 megabecquerel [MBq]) dose of carbon 14-labeled S-649266 ([^{14}C]-S-649266) in healthy adult male subjects. • To quantitate total radioactivity S-649266 equivalent concentrations in whole blood and plasma and S-649266 concentrations in plasma after intravenous administration of a single 1000 mg (~100 µCi) dose of [^{14}C]-S-649266 in healthy adult male subjects. • To examine the metabolism of S-649266 in humans and identify metabolites of S-649266 in plasma, urine, and feces after intravenous administration of a single 1000 mg (~100 µCi) dose of [^{14}C]-S-649266 in healthy adult male subjects. Secondary objective: • To evaluate the safety and tolerability of S-649266 after intravenous administration of a 1000 mg (~100 µCi) dose of [^{14}C]-S-649266 in healthy adult male subjects.		
Study Design: A Phase 1, single-center, open-label, non-randomized, single-dose study in healthy adult male subjects.		

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Number of Subjects (Planned and Analyzed):

Number of subjects planned: 6

Number of subjects enrolled: 6

Number of subjects analyzed for pharmacokinetics: 6

Number of subjects analyzed for safety: 6

Diagnosis and Main Criteria for Inclusion:

This study enrolled healthy male subjects aged 19 to 50 years, inclusive, with a body mass index (BMI) of 18.5 to 30 kg/m^2, inclusive.

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

Test Product: [^{14}C]-S-649266 (0.1 μCi/mg)

Dose and Mode of Administration: Each subject was to receive a 1000 mg (~100 μCi) dose of [^{14}C]-S-649266 as a 100 mL (10 mg/mL) infusion solution administered intravenously over 1 hour. The actual dose administered ranged from 855.01 mg (89.78 μCi) to 947.11 mg (99.45 μCi).

Lot Numbers: [redacted]

Duration of Treatment:

Each subject received a single 1-hour infusion of [^{14}C]-S-649266.

Reference Therapy: Not applicable.

Criteria for Evaluation:

Collection of Blood, Urine and Fecal Samples for Pharmacokinetic Analysis:

Blood samples for determination of plasma and whole blood total radioactivity S-649266 equivalent concentrations (also hereafter referred to as total radioactivity) and for analysis of plasma S-649266 concentrations were collected predose and 0.5, 1 (just prior to the end of the infusion), 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours post-initiation of the infusion (minimum sampling schedule), with additional samples to be potentially collected, until CRU discharge criteria were met, 120, 144, 168, 192, 216, 240, 264, 288, 312, and 336 hours post-initiation of the infusion.

Blood samples for metabolic profiling in plasma were obtained predose and 1, 2, 4, 8, 12, 16, 24, 48, 72, and 96 hours post-initiation of the infusion.

Blood samples for determination of the association of total radioactivity in red blood cells (RBCs) using serial hematocrit values were obtained at 1, 4, 16, 24, and 72 hours post-initiation of the infusion.

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Urine samples for determination of the amount of total radioactivity excreted into urine and metabolic profiling in urine were collected predose from -12 to 0 hours and post-initiation of infusion from 0 to 6 hours, 6 to 12 hours, and 12 to 24 hours on Day 1, and subsequently every 24 hours from Day 2 up to Day 15, as appropriate.

Fecal samples for determination of the amount of total radioactivity excreted into feces and metabolic profiling in feces were collected predose from -24 to 0 hours and post-initiation of the infusion over consecutive 24-hour intervals from Day 1 up to Day 15, as appropriate.

Bioanalytical Assessments:

Whole blood, plasma, urine, and fecal samples were analyzed for total radioactivity using liquid scintillation counting (LSC) at Celerion (Lincoln, Nebraska). The lower limit of quantification (LLOQ) for total radioactivity in plasma and whole blood was 0.4826 µg eq/mL and 0.8893 µg eq/g, respectively. The LLOQ for total radioactivity in urine was 0.2643 µg eq/g for Subjects [redacted] and 1.9024 µg eq/g for Subject [redacted] The LLOQ for total radioactivity in feces was 0.4445 µg eq/g for Subjects [redacted] and 3.4534 µg eq/g for Subject [redacted]

Plasma samples were analyzed for S-649266 concentrations using high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) methods at QPS, LLC (Newark, Delaware). The LLOQ for S-649266 in plasma was 0.1 µg/mL.

Plasma samples were analyzed for identification and profiling of [^{14}C]-S-649266 metabolites by HPLC-MS/MS coupled with a radio flow-through detector at QPS, LLC (Newark, Delaware). Urine and fecal samples were also analyzed for identification and profiling of metabolites.

Pharmacokinetic Parameters:

Plasma and Whole Blood Total Radioactivity S-649266 Equivalent and Plasma S-649266 Concentrations: Area under the concentration-time curve (AUC) from time 0 to the time of the last quantifiable sample after dosing ($AUC_{0\text{-last}}$), AUC from time 0 extrapolated to infinity ($AUC_{0\text{-inf}}$), percentage of $AUC_{0\text{-inf}}$ which was extrapolated ($AUC_{\%extr}$), maximum observed concentration (C_{max}), time to the maximum concentration (T_{max}), time to the last quantifiable sample after dosing (T_{last}), apparent terminal elimination rate constant (λ_z), apparent terminal elimination half-life ($t_{1/2,z}$), apparent total clearance (CL) and apparent volume of distribution during the terminal elimination phase (V_z). The ratios of C_{max} and $AUC_{0\text{-inf}}$ for plasma S-649266 to total radioactivity were calculated.

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Urinary total radioactivity: Amount of total radioactivity excreted in urine during each collection interval (A_{eu}), cumulative amount of total radioactivity excreted in urine, calculated for each collection interval ($CumA_{eu}$), percentage of the administered dose recovered in urine during each collection interval ($\%F_{eu}$), and cumulative percentage of the administered dose recovered in urine, calculated for each collection interval ($Cum\%F_{eu}$), and for total radioactivity in feces: Amount of total radioactivity excreted in feces during each collection interval (A_{ef}), cumulative amount of total radioactivity excreted in feces, calculated for each collection interval ($CumA_{ef}$), percentage of the administered dose recovered in feces during each collection interval ($\%F_{ef}$), and cumulative percentage of the administered dose recovered in feces, calculated for each collection interval ($Cum\%F_{ef}$).

Safety Assessment:

Safety evaluations were based on the incidence, severity, and type of adverse events (AEs) and on clinically meaningful changes or abnormalities in vital sign measurements, electrocardiogram (ECG) parameters, physical examination, and clinical laboratory tests.

Statistical Methods:

Pharmacokinetics:

The whole blood and plasma total radioactivity and plasma S-649266 PK parameter ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{\%extr}$, C_{max}, λ_z, $t_{1/2,z}$, CL, V_z, ratios of C_{max} and $AUC_{0\text{-inf}}$ [except for T_{max} and T_{last}]) values and urinary and fecal total radioactivity PK parameter (A_{eu}, $CumA_{eu}$, $\%F_{eu}$, $Cum\%F_{eu}$, A_{ef}, $CumA_{ef}$, $\%F_{ef}$, and $Cum\%F_{ef}$) values were listed by parameter for each analyte and matrix, and summarized using the following descriptive statistics: sample size (n), arithmetic mean, standard deviation (SD), coefficient of variation as a percentage (CV%), median, minimum (min), maximum (max), geometric mean (GM), and geometric CV%.

The whole blood and plasma T_{max} and T_{last} for total radioactivity and plasma S-649266 were summarized using the following descriptive statistics: n, arithmetic mean, SD, CV%, median, min, and max.

Safety:

Adverse events were classified by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA®, Version 18.1). All AEs were collected, regardless of whether they presented before or after study drug administration. Summary statistics for ECG parameters at each scheduled time point and for the change from baseline to each time point are provided. Baseline was the

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result obtained at check-in (Day -1). Fridericia's correction formula was used to calculate the QTc interval.

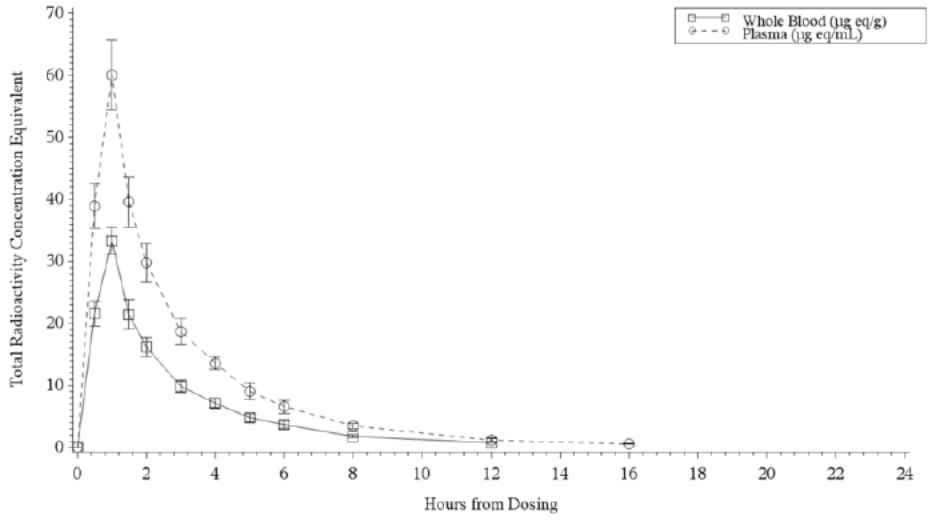
Summary of Results

Pharmacokinetics:

Plasma and Whole Blood Total Radioactivity S-649266 Equivalent and Plasma S-649266 Concentrations

The mean plasma total radioactivity S-649266 equivalent (total radioactivity) concentrations were approximately 2 times higher than in whole blood total radioactivity across all sampling time points (Figure 1). Overall, the shapes of the mean total radioactivity concentration-time profiles were similar in both matrices, with peak mean concentration that corresponded to end of the infusion and relatively parallel rates of post-peak decline. The mean plasma S-649266 concentration- and total radioactivity S-649266 equivalent concentration-time profiles also exhibited relatively similar shapes, but peak mean plasma S-649266 concentrations were higher than total radioactivity concentrations (Figure 2).

Figure 1 **Arithmetic Mean (SD) Whole Blood and Plasma Total Radioactivity S-649266 Equivalent Concentration-Time Profiles (Linear Scale)**



[redacted]

Source: Figure 14.2.2.1.1

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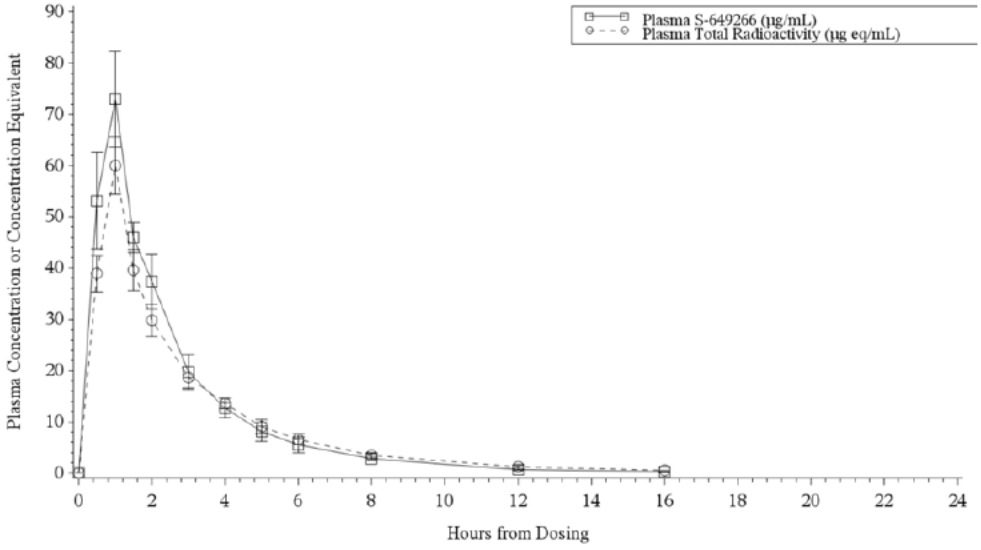
Figure 2 **Arithmetic Mean (SD) Plasma S-649266 and Total Radioactivity S-649266 Equivalent Concentration–Time Profiles (Linear Scale)**



[redacted]

Source: Figure 14.2.2.1.3

Plasma and Whole Blood Total Radioactivity S-649266 Equivalent and Plasma S-649266 Pharmacokinetic Parameters

The mean exposure-relevant plasma total radioactivity and S-649266 PK parameters were generally similar (Table 1). However, the geometric mean (GM) plasma C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ values for S-649266 were higher than the corresponding plasma parameter values for total radioactivity, resulting in GM ratios (GMR; S-649266/total radioactivity) for the plasma C_{max} and $AUC_{0\text{-inf}}$ were 1.219 and 1.086, respectively.

The GM whole blood C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ values for total radioactivity were nearly half of the corresponding plasma parameter values for total radioactivity, a result that approximates the physiologic ratio of plasma to blood volume (i.e., approximately 1 – hematocrit), indicating that total radioactivity was predominantly associated with plasma, with little partitioning into red blood cells (RBCs) (Table 2). This was further supported by the results from the analysis of the association of total radioactivity with RBCs at the 1 and 4-hour post-initiation of the infusion time points (the only time points where these assessments could be made, i.e., where total radioactivity S-649266 equivalent concentrations were quantifiable in both whole

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blood and plasma), which shows that the mean partitioning values were less than zero, indicating absence of any partitioning of total radioactivity into RBCs.

The median T_{max} values for whole blood and plasma total radioactivity and plasma S-649266 were similar, and corresponded to the end of 1-hour infusion of [^{14}C]-S-649266. The GM $t_{1/2,z}$ values were relatively short and comparable across the analytes/matrices, and were 2.14 hours and 2.73 hours for whole blood and plasma total radioactivity , respectively, and was 2.29 hours for plasma S-649266 in plasma. The median T_{last} value (16.00 hours) was the same for plasma total radioactivity and S-649266, but was approximately half (8.02 hours) for whole blood total radioactivity. Consistent with the similar and short $t_{1/2,z}$ values and the respective T_{last} values, the $AUC_{\%extr}$ for plasma S-649266 and total radioactivity were negligible (0.5% and 1.7%, respectively) and greater for whole blood total radioactivity (5.7%).

The GM CL and V_z values for S-649266 in plasma (5.28 L/hr and 17.5 L, respectively) were relatively similar to those for total radioactivity in plasma (5.73 L/hr and 22.6 L, respectively), for which CL values were approximately one half and V_z values one half to one third lower than the corresponding values whole blood for total radioactivity (10.8 L/hr and 33.2 L, respectively).

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Table 1 **Summary of the Pharmacokinetic Parameters for Total Radioactivity in Plasma and Whole Blood and S-649266 in Plasma After Intravenous Administration of a Single 1000 mg (~100 µCi) Dose of [^{14}C]-S-649266 Infused Over 1 Hour**

		Whole Blood Total Radioactivity	Plasma Total Radioactivity	Plasma S-649266
Pharmacokinetic Parameters	**n**	**GM (GCV%)**	**GM (GCV%)**	**GM (GCV%)**
C_{max} (µg/mL)[a]	6	33.3 (6.5)	59.8 (9.3)	72.9 (12.4)
T_{max} (hr)[c]	6	0.98 (0.98, 1.00)	0.99 (0.98, 1.01)	0.97 (0.50, 1.00)
T_{last} (hr)[c]	6	8.02 (8.00, 12.00)	16.00 (12.01, 16.01)	16.00 (15.99, 16.00)
$AUC_{0\text{-}last}$ (µg*hr/mL)[b]	6	79.26 (8.7)	155.4 (10.0)	170.8 (8.4)
$AUC_{0\text{-}inf}$ (µg*hr/mL)[b]	6	84.26 (8.9)	158.0 (9.8)	171.7 (8.4)
$AUC_{\%extr}$ (%)	6	5.7 (31.7)	1.7 (13.9)	0.5 (37.2)
λ_z (1/hr)	6	0.3239 (15.1)	0.2539 (14.5)	0.3021 (9.5)
$t_{1/2,z}$ (hr)	6	2.14 (15.1)	2.73 (14.5)	2.29 (9.5)
CL (L/hr)	6	10.8 (6.9)	5.73 (7.6)	5.28 (7.3)
V_z (L)	6	33.2 (16.8)	22.6 (14.9)	17.5 (13.9)
Ratio C_{max}[d]	6	NC	NC	1.219 (15.3)
Ratio AUC[e]	6	NC	NC	1.086 (4.5)

a µg·eq/mL for plasma total radioactivity and µg·eq/g for whole blood total radioactivity
b µg·eq*hr/mL for plasma total radioactivity and µg·eq*hr/g for whole blood total radioactivity
c T_{max} and T_{last} are presented as Median (Minimum, Maximum).
d Ratio C_{max} = plasma S-649266 C_{max}/plasma total radioactivity C_{max}.
e Ratio AUC = plasma S-649266 $AUC_{0\text{-}inf}$/plasma total radioactivity $AUC_{0\text{-}inf}$.
GM = Geometric mean; GCV% = Geometric coefficient of variation %; eq = Equivalents; NC = Not calculated
Source: Tables 14.2.1.1.3, 14.2.1.1.4, 14.2.1.2.2 and 14.2.1.2.3

Table 2 **Summary of Association of Total Radioactivity With Red Blood Cells After Intravenous Administration of a Single 1000 mg (~100 µCi) Dose of [^{14}C]-S-649266 Infused Over 1 Hour**

Sample Time (hr)	n	Mean ± SD
1	6	-7.3 ± 2.3
4	5	-11.4 ± 4.2

The association of total radioactivity with red blood cells (%) = ([C_b - {C_p x (1 - Hct)}]/C_b) x 100 where C_b = total radioactivity S-649266 equivalent concentration in whole blood; C_p = total radioactivity S-649266 equivalent concentration in plasma; and Hct = hematocrit value expressed as a fraction

Source: Table 14.2.1.1.7

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Excretion of Total Radioactivity in Urine and Feces and Assessment of Mass Balance

The amount of total radioactivity excreted in urine and feces and mass balance calculations were based on the actual dose administered to each subject, and showed a GM recovery of 919 mg equivalents of S-649266 that corresponds to a GM recovery of 101.44% of the administered dose (Figure 3 and Table 3).

Total radioactivity was primarily (GM: 98.59%) excreted in urine, with a minor amount (GM: 2.79%) excreted into the feces. The majority of total radioactivity was excreted within the first 24 hours postinitiation of the infusion (GM of 96.06% for urine and feces combined). Urinary excretion was complete (i.e., concentrations in subsequent 24-hour collection intervals were below LLOQ) by either 48 hours (n = 3) or 72 hours (n = 3) post-initiation of the infusion, and fecal excretion was complete (i.e., concentrations in subsequent 24-hour collection intervals were below LLOQ) by 72 hours (n = 2) or 96 hours (n = 4) post-initiation of the infusion.

Figure 3 **Arithmetic Mean (SD) Cumulative Percent of [^{14}C]-S-649266 Dose Excreted Based on Total Radioactivity in Urine, Feces, and Total Versus Endpoint of the Collection Interval (Linear Scale)**

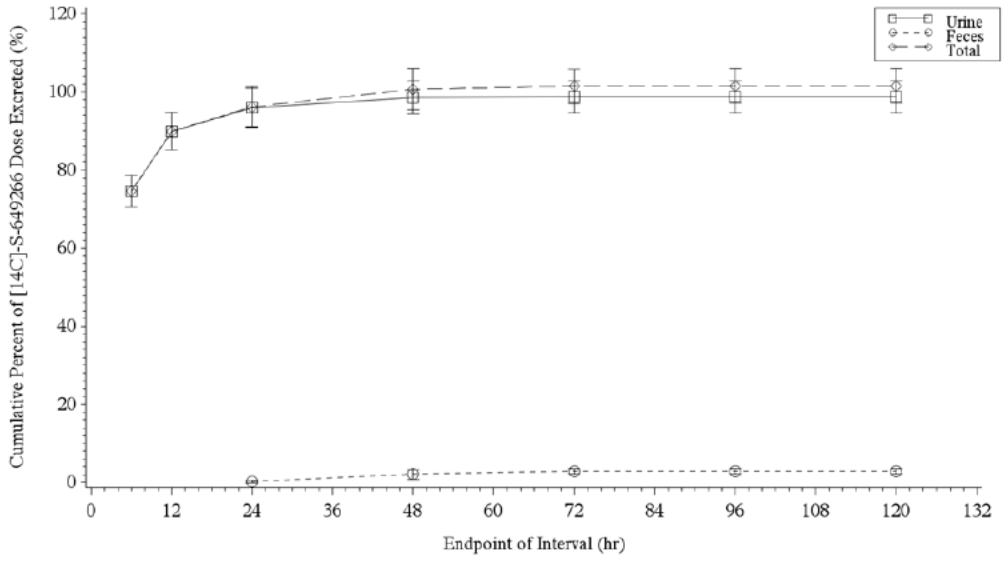

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Table 3 **Summary of Total Radioactivity Excreted and Mass Balance After Intravenous Administration of a Single 1000 mg (~100 µCi) Dose of [^{14}C]-S-649266 Infused Over 1 Hour**

		Urine	Feces	Total
Pharmacokinetic Parameters	**n**	**GM (CV%)**	**GM (CV%)**	**GM (CV%)**
CumAe (mg eq)	6	893 (4.1)	25.3 (24.4)	919 (4.3)
Cum%Fe (%)	6	98.59 (4.1)	2.79 (25.1)	101.44 (4.4)

CumAe = Cumulative amount of total radioactivity excreted expressed in mg eq of parent drug
Cum%Fe = Cumulative fraction of dose of parent drug excreted expressed as a percentage of the administered dose
eq = Equivalents
Source: Table 14.2.1.3.4

[redacted]

Metabolite Profiling

A total of twenty-one (21) S-649266-related components (M1 to M21) were detected in plasma, urine, or feces. M1 to M12 and M14 to M18 were characterized using HPLC-MS/MS. M13 and M19 to M21 could not be characterized due to low concentrations. M14 to M18 were also detected in the test article (S-649266 powder for solution provided as a reference substance) and therefore might have been impurities in the test article. S-649266 was the predominant peak in the plasma radiochromatograms for each of the pooled 1-, 2-, 4-, 8-, and 12-hour postdose time points. Minor peaks, designated as M2, M3, M9, and M14 to M17, were observed in the plasma radiochromatograms for the pooled 1-, 2-, and 4-hour post-initiation of infusion time points. S-649266 was the predominant peak in urine radiochromatograms for all 6 subjects. Minor peaks, designated as M2 to M4, M6, and M8 to M13, were observed in urine radiochromatograms. Metabolites M2 and M8 were the predominant peaks in the fecal radiochromatograms. Minor peaks, designated as M7, M11, M12, and M19 to M21, were observed in the fecal radiochromatograms.

The metabolic pathways of S-649266 include N-dealkylation, epimerization, methylation, glucuronidation, and sulfation. N-dealkylation of the pyrrolidine nitrogen of S-649266 produces M2 which undergoes glucuronidation and sulfation to form M1 and M4, respectively. The 2 hydroxyl groups on the catechol moiety of M2 are also methylated to form M7 and M8, which are further glucuronidated to form M3 and M6, or sulfated to form M5 and M9. O-methylation of the catechol moiety of S-649266 produces M11 and M12. S-649266 is also epimerized to form M10.

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S-649266 was the major radioactive component in each subject and accounted for 92.27% of the plasma AUC_{0-16} for total radioactivity. M2 accounted for 4.70%, M3 and M9 accounted for < 0.5%, and M14 to M16, which may be impurities, each accounted for < 2% of the plasma AUC_{0-16} for total radioactivity. S-649266 was the major radioactive component in urine and accounted for 90.57% of the administered dose. M3, M6, and M9 each accounted for 1 to 3% of the administered dose. M2, M4, M8, and M10 to M13 each accounted for < 1% of the administered dose. M2 was the predominant radioactive component in feces and accounted for 1.69% of the administered dose. M7, M8, M11, and M12 each accounted for < 1% of the administered dose. M19 to M21 each accounted for < 0.02% of the administered dose.

Safety:

No deaths, SAEs, or AEs resulting in withdrawal from the study were reported. Only a single TEAE of epistaxis was reported by one subject that was rated as mild and considered by the investigator not to be related to study drug.

No clinically meaningful abnormalities in ECG parameters, vital sign measurements, or clinical laboratory tests were observed.

These findings indicate that a single 1000 mg (~100 μCi) dose of [^{14}C]-S-649266 administered intravenously over 1 hour in healthy adult male subjects was generally safe and well tolerated.

CONCLUSIONS

Pharmacokinetics:

- Mass balance for S-649266 was achieved as evidenced by a GM recovery of total radioactivity of 101.44% of the administered dose in urine and feces combined. For all subjects, the majority of total radioactivity (GM of 96.06%) was excreted within the first 24 hours and complete elimination was achieved by 96 hours post-initiation of infusion.
- Renal excretion was the major route of elimination for the total radioactivity (GM of 98.59%), with the excretion of total radioactivity into feces comprising a minor route of elimination (GM of 2.79%).
- The GM values for C_{max}, AUC_{0-last}, and AUC_{0-inf} of total radioactivity and S-649266 in plasma were similar, indicating that virtually all the radioactivity in plasma is associated with intact S-649266.
- Total radioactivity was predominantly associated with plasma, with little partitioning into RBCs.

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- A total of twenty-one (21) S-649266-related components (M1 to M21) were detected in plasma, urine, or feces. The metabolic pathways elucidated for S-649266 include N-dealkylation, epimerization, methylation, glucuronidation, and sulfation.
- S-649266 was the major radioactive component in plasma in all subjects and accounted for 92.27% of the plasma AUC_{0-16} for total radioactivity. The M2 component accounted for 4.70%, the M3 and M9 components accounted for < 0.5%, and the M14, M15, and M16 components, which may be impurities, each accounted for < 2% of the plasma AUC_{0-16} for total radioactivity.
- S-649266 was the major radioactive component in urine and accounted for 90.57% of the administered dose. The M3, M6, and M9 components each accounted for 1 to 3% of the administered dose. The M2, M4, M8, M10, M11, M12, and M13 components each accounted for < 1% of the administered dose.
- The M2 component was the predominant radioactive component in feces and accounted for 1.69% of the administered dose. The M7, M8, M11, and M12 components each accounted for < 1% of the administered dose. The M19, M20, and M21 components each accounted for < 0.02% of the administered dose.

Safety:

- Intravenous administration of a single 1000 mg (~100 μCi) dose of [14C]-S-649266 infused over 1 hour in healthy adult male subjects was generally safe and well tolerated.

Report Date: 16 May 2017