2 SYNOPSIS

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Study Title: An Open-label, Non-Randomized Study to Evaluate the Pharmacokinetics, and Safety and Tolerability of S-649266 in Subjects with Varying Degrees of Renal Impairment and in Matched Control Subjects With Normal Renal Function

Investigators and Study Centers:

[redacted]

Publication (reference): None

Studied Period:

[redacted] February 2014 (first subject enrolled) to [redacted] August 2014 (last subject completed)

Study Phase: Phase 1

Objectives:

The primary objectives of the study:

- Pharmacokinetics (PK) of S-649266 in subjects with mild, moderate, and severe renal impairment, and subjects undergoing hemodialysis (HD)
- Effect of HD on elimination of S-649266 from blood

The secondary objective of the study:

- Safety and tolerability of S-649266 following intravenous (IV) dose administration in all subjects
- Pharmacokinetics of S-649266 in subjects with normal renal function

Methodology:

This was an open-label, non-randomized, and parallel cohort study. A total of 38 subjects were enrolled in 5 cohorts (8 subjects in each cohort except Cohort 4 in which 6 subjects were enrolled). After a Screening Period of 27 days (Day -28 to Day -2 relative to Day 1), subjects meeting the eligibility criteria, (with mild, moderate, and severe renal impairment as estimated by Modification of Diet in Renal Disease [MDRD] criteria, subjects undergoing HD, and matched control healthy subjects with normal renal function as estimated by Cockcroft-Gault criteria), were enrolled in respective cohorts. The subjects were admitted to the clinical research unit (CRU) on Day -1 for the duration of their participation in the study with the exception of subjects

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on HD who were released between treatment periods. On Day 1, subjects received a single IV administration of the study drug, after at least 8 hours of fasting. In the absence of a clinical concern, subjects were discharged from the CRU in the morning of Day 4, after completion of all procedures scheduled for 72 hours postdose time point. Subjects returned for a final Follow-up Visit within approximately 14 days after discharge. Cohort 5 subjects received 2 dosing sessions. The first dose was administered after an HD session, followed by the blood sampling at prescribed time points for the cohorts with renally impaired subjects. The second dose was administered following at least a 72-hour washout and was given approximately 2 hours prior to the subject's HD session. Cohort 5 subjects could remain in the CRU between doses, although, this was not mandatory, until the completion of the safety evaluations following the final HD treatment.

Listing of Cohorts

- Cohort 1: Eight healthy control subjects (estimated creatinine clearance [CL_{cr}] $\geq$ 90 mL/min) demographically matched to the moderate renal impairment group for age (± 10 years), body mass index (BMI) (± 20%), and gender
- Cohort 2: Eight subjects with mild renal impairment (estimated glomerular filtration rate [eGFR] $\geq$ 60 and < 90 mL/min/1.73 m^2)
- Cohort 3: Eight subjects with moderate renal impairment (eGFR $\geq$ 30 and < 60 mL/min/1.73 m^2)
- Cohort 4: Six subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m^2)
- Cohort 5: Eight subjects with end-stage renal disease treated by HD

Enrollment of severe renal impairment subjects (Cohort 4) was completed in 6 subjects after considerable effort.

Prohibited Therapies or Restrictions

Prohibited Therapies

Healthy Subjects

- The use of prescription or non-prescription medications, any over-the-counter medication, including herbal medicine or dietary supplements, within 14 days prior to dosing and during the entire study
- Any drug administered during the 72-hour before the start of dosing

Restrictions

- Subjects were instructed not to donate blood during the study, subjects who had

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donated more than 400 mL of blood within 12 weeks or 200 mL within 4 weeks prior to the Screening Visit were excluded from the study.

- Foods and beverages containing alcohol, red wine, Seville oranges, grapefruit or grapefruit juice, pomelo, exotic citrus fruits, or grapefruit hybrids or fruit juices containing such products were not allowed from 7 days prior to admission until completion of the end-of-study (EOS)/Early Termination Visit.
- Foods and beverages containing caffeine were not allowed from 72 hours prior to admission until completion of the EOS/Early Termination Visit.
- Subjects in the normal healthy group (Cohort 1) were not allowed to smoke. Smoking-cessation aids were not permitted.
- Strenuous exercises were prohibited from 3 days prior to Screening through the completion of Screening and from 3 days prior to admission to the site to the completion of study/early termination assessments.

Number of Subjects (Planned and Analyzed):

Number of subjects planned: Eight subjects each in Cohorts 1, 2, 3, and 5, and 4 to 8 subjects in Cohort 4.

Number of Subjects Enrolled: 38 (8 subjects each in Cohorts 1, 2, 3, and 5, and 6 subjects in Cohort 4)

Number of subjects analyzed for PK concentration: 38

Number of subjects analyzed for PK parameter: 37 (8 subjects each in Cohorts 1, 2, and 5, 7 subjects in Cohort 3, and 6 subjects in Cohort 4)

Number of subjects analyzed for safety: 38

Diagnosis and Main Criteria for Inclusion:

Main Criteria for Inclusion

<u>All Subjects</u>

- Men and women aged 20 to 80 years at the time of signing informed consent with a BMI between 18.5 and 38.0 kg/m^2 (inclusive).

<u>Healthy Subjects</u>

- Each healthy subject was matched to the demographic characteristics of 1 subject with moderate renal impairment with respect to age (± 10 years), BMI (± 20%), and gender. One healthy subject was matched to each subject with moderate renal impairment.

<u>Subjects With Renal Impairment</u>

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- Subjects that were not undergoing HD with mild, moderate, or severe renal impairment based upon their MDRD creatinine clearance estimate (ie, eGFR) calculated at Screening.

Subjects Undergoing Hemodialysis

- Subjects receiving stable HD at least 3 times a week for at least 6 months and with clinically stable condition with respect to underlying renal impairment.

Main Criteria for Exclusion

- Subjects with fluctuating or rapidly deteriorating renal function were excluded from the study.
- Subjects who required continuous treatment with methotrexate, procainamide, probenecid, or valproic acid were excluded from the study.

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

Test Product: S-649266

Dose and Mode of Administration:

Cohorts 1 to 4: single 1000 mg IV dose over 1 hour

Cohort 5: Two doses, each of 1000 mg, intravenously administered over 1 hour, first dose after the HD session and second dose 2 hours before the HD session, with minimum 72 hours washout in between.

Lot Number: [redacted] **Packaged Lot Number**: [redacted]

Duration of Treatment:

Subjects with Normal Renal Function and Mild, Moderate, and Severe Renal Impairment (Cohorts 1 to 4):

Screening Period (Day -28 to Day -2): Up to 27 days

Confinement in CRU (Day -1 to 4): Four nights, 5 days

Days of Drug Administration (Day 1): One day

Follow-up Period: 14 days ± 1 after last discharge from CRU

Total planned study conduct per subject: approximately 3 to 6.5 weeks

Subjects on Hemodialysis (Cohort 5)

Screening Period (Day -28 to Day -2): Up to 27 days

Confinement in CRU (Day 1): Two separate sessions of 4 nights, 5 days for a total of 8 nights and 10 days

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Days of drug administration (Day 1): Two separate days that fit study requirements for washout and the subject's HD schedule

Follow-up Period: 14 days ± 1 after last discharge from CRU

Total planned study conduct per subject: Approximately 5 to 8 weeks

Reference Therapy:
Not applicable

Criteria for Evaluation:

Pharmacokinetic Analysis:

Pharmacokinetic parameters were calculated based on the plasma and urine concentrations by using model independent approaches.

Plasma Pharmacokinetic Parameters:

Blood for PK analysis was collected immediately before (-0.25 hour) and during infusion at 0.25, 0.5 and 1 hour (at the end of infusion) and at 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours from the start of infusion. The actual sampling times were used in the parameter calculations, and PK parameters were derived using standard non-compartmental analysis method in Phoenix WinNonlin® version 6.3. The PK parameters included maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration after dosing ($AUC_{0\text{-}last}$), area under the plasma concentration-time curve extrapolated from time zero to infinity ($AUC_{0\text{-}inf}$), apparent terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2,z}$), total clearance (CL), and volume of distribution at steady state (V_{ss}).

The individual subject plasma concentration-time data were listed and displayed graphically on the linear and log scales and were summarized descriptively using tabular and graphical formats (linear and semi-logarithmic scales) by cohort based on renal function. Plasma concentration of the 1000-mg dose of S-649266 was summarized for cohort based on renal function by nominal sample time by the following summary statistics: Number of non-missing observations (n), arithmetic mean, standard deviation (SD), coefficient of variation (CV%), geometric mean (GM), and CV% for GM, median, minimum, maximum, and number of observation < lower limit of quantification (LLOQ).

Protein Binding of Plasma S-649266:

Plasma protein unbound fraction (Fu) of S-649266 was determined for PK blood samples collected at 1 hour (end of infusion) and 8 hours after the start of the infusion

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for Cohorts 1 to 4 and the first period for Cohort 5.

Urine Pharmacokinetic Parameters:

Urine samples for PK analysis were collected at predose and then postdose over the intervals 0 to 8, 8 to 16, 16 to 24, 24 to 36, 36 to 48, and 48 to 72 hours for subjects that could produce urine. Urine PK parameters for the 1000-mg dose of S-649266 included: cumulative amount of the drug excreted in urine (Aeu_{0-72}), urinary excretion ratio (Feu_{0-72}), and renal clearance (CL_R). For Cohorts 4 and 5, subjects' urine PK samples were collected when possible.

The summary statistics (excluding number of observations) used for plasma concentration, were presented for analyses of plasma and urine PK parameters.

Hemodialysis Sampling for Cohort 5

During HD, the PK arterial and venous samples and aliquots from the dialysate were collected at the following time points relative to the start of HD: 3, 4, 5, and 6 hours or at the end of HD. For subjects on HD, HD clearance (CLhd) and the fraction of the total body pool of drug removed by HD (Fr) were determined.

Bioanalytical Assessment:

Blood and urine samples for PK analyses were collected at protocol specified time points in the study.

Safety Assessment:

The safety and tolerability of S-649266 were assessed by monitoring of adverse events (AEs), physical examinations including brief neurological examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature, respiration rate and mean arterial pressure [MAP]), 12-lead electrocardiograms (ECGs) including continuous cardiac monitoring, and clinical laboratory assessments (including hematology, blood chemistry tests, and urinalysis). The AEs were recorded and treatment-emergent AEs (TEAEs), adverse drug reactions (ADRs; defined as AEs related to study drug), significant AEs, and serious AEs (SAEs) were listed.

Statistical Methods:

Pharmacokinetics:

Pharmacokinetic parameters of S-649266 were calculated based on the plasma and urine concentrations of S-649266 by using model independent approaches. An analysis of variance (ANOVA) model was used to perform the statistical analysis of PK parameter with log transformed PK parameters C_{max}, AUC_{0-last}, AUC_{0-inf}, λ_z, $t_{1/2,z}$, CL, V_{ss}, and CL_R as response variable and with fixed effect terms for renal function

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level (normal renal function, mild, moderate, and severe renal impairment, and HD [dosing after HD, ie, non-dialysis period]).

The point estimates and their associated 90% confidence interval (CI) were constructed for the differences, mild renal impaired versus normal renal function, moderate renal impaired versus normal renal function, severe renal impaired versus normal renal function, and HD (non-dialysis period) versus normal renal function. The point estimates and 90% CI were then back-transformed to give point estimates and 90% CI for the ratio of the parameters in subjects with mild, moderate, severe renal impairment, and subjects treated by HD (non-dialysis period) compared with healthy control subjects.

Safety

The number of AEs and the number of subjects who experienced any AEs were summarized by treatment group and the incidence was calculated. The same summarization and calculation were performed for ADRs. Summary statistics for vital signs (blood pressure, pulse rate, respiration rate, and body temperature), ECG evaluations (heart rate, QRS, QT, PR, and QT interval corrected for heart rate [QTc], Bazett's correction for QT [QTcB] and Fridericia's correction for QT [QTcF] intervals), and laboratory test evaluations (hematology, blood chemistry, and urinalysis) were calculated.

Summary of Results

Pharmacokinetics:

PK data analysis was conducted with or without the 7 anomalous plasma concentrations. Results from the data set with anomalous values excluded were the primary analyses data for this study and are discussed in this synopsis.

Plasma PK parameter estimate values from each cohort are presented in Table 1. Summary plots of S-649266 plasma concentrations versus time are shown Figure 1.

Table 1 Pharmacokinetic Parameters Estimates Summarized for Each Cohort

Cohort	Renal Function		C_{max} µg/mL	T_{max} hr	$AUC_{0\text{-last}}$ µg•hr/mL	$AUC_{0\text{-inf}}$ µg·hr/mL	$t_{1/2,z}$ hr	CL L/hr	V_{ss} L
		n	8	8	8	8	8	8	8
1	Normal	GM*	81.0		212.0	213.4	2.82	4.69	13.5
		GM CV%	27.4		26.7	26.5	16.5	26.	30.

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								5	2
		Min		1.00					
		Median		1.00					
		Max		1.03					
2	Mild Impairment	n	8	8	8	8	8	8	8
		GM	73.4		217.8	218.7	2.98	4.57	14.8
		GM CV%	21.3		22.2	22.2	8.4	22.2	17.7
		Min		1.00					
		Median		1.00					
		Max		1.00					
3	Moderate Impairment	n	7	7	7	7	7	7	7
		GM	78.0		311.0	312.3	4.13	3.20	15.4
		GM CV%	31.1		38.6	38.4	12.6	38.4	28.7
		Min		1.00					
		Median		1.00					
		Max		1.00					
4	Severe Impairment	n	6	6	6	6	6	6	6
		GM	80.1		540.3	543.2	6.91	1.84	16.4
		GM CV%	19.8		23.6	23.6	30.6	23.6	23.4
		Min		1.00					
		Median		1.00					
		Max		1.07					
5	Hemodialysis (Period 1, non-dialysis period)	n	8	8	8	8	8	8	8
		GM	93.0		872.5	880.7	9.60	1.14	14.2
		GM CV%	27.8		23.9	24.2	33.4	24.2	22.5
		Min		1.00					
		Median		1.00					
		Max		1.02					
5	Hemodialysis (Period 2, dialysis	n	8	8	8	8	8	8	8
		GM	75.4		314.9	318.1	9.45	3.1	26.

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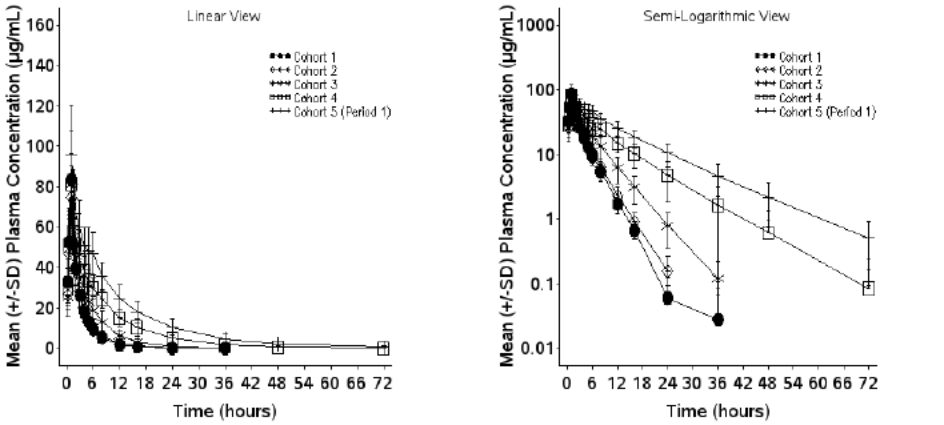
period)						4	6
GM CV%	31.1		20.3	20.3	32.8	20.3	33.5
Min		1.00					
Median		1.00					
Max		1.53					

Abbreviations: CV%, coefficient of variation; GM, geometric mean; HD, hemodialysis; max, maximum; min, minimum.

* Geometric mean calculated using log transformed data.GM CV%=SQRT[exp(sd^2)-1] × 100, where sd was the standard deviation for natural log (ln)-transformed data.

Figure 1 **Mean ± SD S-649266 Plasma Concentrations versus Nominal Time**



Cohort 1: Matched healthy subjects with normal renal function, Cohort 2: Subjects with mild renal impairment, Cohort 3: Subjects with moderate renal impairment, Cohort 4: Subjects with severe renal impairment, Cohort 5 (Period 1): Subjects with end stage renal disease (ESRD) treated by hemodialysis
SD - Standard Deviation; Cohort 3 subject [redacted] was excluded as the subject discontinued before completion of infusion.
Extreme values for Cohort 4 subjects, [redacted] at 0.25 hrs and [redacted] at 0.25 & 0.5 hrs, and for Cohort 5 subject, [redacted] at 0.25 hrs are excluded from calculation of Arithmetic mean and SD.

Impact of Hemodialysis on S-649266 Plasma Pharmacokinetic in Subjects Treated by Hemodialysis (Samples Drawn Before, During and After Dialysis)

Hemodialysis removed S-649266 in plasma (Fr) by 62.3% (8.4%) [GM (GM CV%)]. The GM (GM CV%) CLhd (primary calculation) was 7.47 L/hr (9.8%). The figure below shows that elimination appeared biphasic due to the removal of study drug during the dialysis period.

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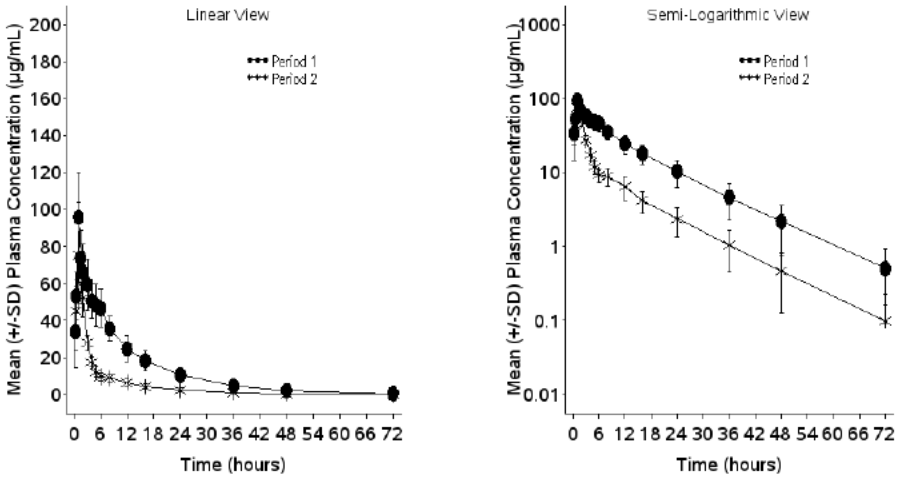
Figure 2 **Mean ± SD S-649266 Plasma Concentrations versus Nominal Time From Subjects Before or Concomitant with Hemodialysis**



Cohort 5: Subjects with end stage renal disease (ESRD) treated by hemodialysis.
SD - Standard Deviation; Extreme values for subject [redacted] on Period 1 at 0.25 hrs and on Period 2 at 0.25 & 0.5 hrs and for subject [redacted] on Period 2 at 0.25 hrs are excluded from calculation of Arithmetic Mean and SD.

Impact of Renal Impairment Status on Plasma Protein Binding

There was no apparent effect of renal function status on S-649266 plasma protein binding. Similar values were observed from subjects in each cohort.

Urinary Pharmacokinetics

Results, shown in Table 2, demonstrated decreased urinary excretion with decreased renal function.

Table 2 **Urinary Excretion Parameter Estimates (GM, GM CV%) for S-649266 by Cohort**

Cohort		Aeu_{0-72} (mg)	Feu_{0-72} (%)	CL_R (L/hr)
1	GM*	686	68.6	3.24
	GM CV%	17.3	17.3	28.0
2	GM	683	68.3	3.14
	GM CV%	14.0	14.0	30.3
3	GM	555	55.5	1.78
	GM CV%	19.6	19.6	41.9
4	GM	260	26.0	0.409

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	GM CV%	43.6	43.6	76.5
5[a] (Period 1)	GM	9.88	0.988	0.0122
	GM CV%	143534.8	143534.8	175476
5[a] (Period 2)	GM	5.13	0.513	0.0125
	GM CV%	2245033.7	2245033.7	24562503.9

a Urinary excretion data was obtained for 4 of the 8 subjects in this cohort.

* Geometric mean calculated using log transformed data.GM CV%=SQRT[exp(sd^2)-1] × 100, where sd was the standard deviation for natural log (ln)-transformed data.

Statistical Analysis of Pharmacokinetic Parameters by Renal Function Level

Statistically significant differences (ie, the 90% CI did not include 1.0) between impaired renal function cohorts and the normal renal function cohort were observed for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, λ_z, $t_{1/2,z}$, CL, and CL_R. Comparisons that differed significantly are denoted with an asterisk in Table 3 below. Thus, worsening renal function significantly impacts 6 of the 8 PK parameters.

Table 3 Impact of Renal Function on Pharmacokinetic Parameters Compared with Normal

Parameter (Unit)	Renal Function Cohort	Geometric Mean	Ratio[a]	90% CI for Ratio[b]
C_{max} (µg/mL)	Normal	81.04		
	Mild	73.37	0.905	0.729 - 1.124
	Moderate	77.99	0.962	0.769 - 1.204
	Severe	80.12	0.989	0.783 - 1.249
	Hemodialysis (non-dialysis period)	93.01	1.148	0.925 - 1.425
$AUC_{0\text{-inf}}$ (µg•hr/mL)	Normal	213.37		
	Mild	218.74	1.025	0.817 - 1.287
	Moderate	312.34	1.464*	1.157 - 1.852
	Severe	543.21	2.546*	1.992 - 3.254
	Hemodialysis (non-dialysis period)	880.70	4.128*	3.289 - 5.181
$AUC_{0\text{-last}}$ (µg•hr/mL)	Normal	211.97		
	Mild	217.77	1.027	0.818 - 1.290
	Moderate	310.97	1.467*	1.159 - 1.857
	Severe	540.31	2.549*	1.993 - 3.260
	Hemodialysis (non-dialysis period)	872.54	4.116*	3.278 - 5.169

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λ_z (1/hr)	Normal	0.25		
	Mild	0.23	0.945	0.786 - 1.137
	Moderate	0.17	0.683*	0.564 - 0.827
	Severe	0.10	0.407*	0.334 - 0.497
	Hemodialysis (non-dialysis period)	0.07	0.293*	0.244 - 0.353
$t_{1/2,z}$ (hr)	Normal	2.82		
	Mild	2.98	1.058	0.879 - 1.272
	Moderate	4.13	1.465*	1.210 - 1.773
	Severe	6.91	2.454*	2.010 - 2.996
	Hemodialysis (non-dialysis period)	9.60	3.409*	2.834 - 4.100
CL (L/hr)	Normal	4.69		
	Mild	4.57	0.975	0.777 - 1.224
	Moderate	3.20	0.683*	0.540 - 0.864
	Severe	1.84	0.393*	0.307 - 0.502
	Hemodialysis (non-dialysis period)	1.14	0.242*	0.193 - 0.304
V_{ss} (L)	Normal	13.52		
	Mild	14.81	1.096	0.891 - 1.348
	Moderate	15.38	1.138	0.918 - 1.410
	Severe	16.36	1.211	0.968 - 1.514
	Hemodialysis (non-dialysis period)	14.16	1.048	0.852 - 1.289
CL_R	Normal	3.24		
	Mild	3.14	0.970	0.323 - 2.912
	Moderate	1.78	0.552	0.177 - 1.722
	Severe	0.48	0.149*	0.045 - 0.488
	Hemodialysis (non-dialysis period)	0.01	0.004*	0.001 - 0.015

a The ratio of the various renal insufficiency groups compared with the normal renal group, ie, renal/normal.

b The ANOVA model included log transformed PK parameters as response variable and fixed effect term as renal function group.

* Ratio not equal to 1.0 (ie, statistically significant difference between cohorts)

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Correlation of S-649266 Pharmacokinetics with Renal Function Status

The best fit of the data was for CL versus CL_{cr} ($R^2 = 0.8430$); eGFR also showed a strong relationship ($R^2 = 0.6293$) although it tended to slightly overestimate S-649266 CL for eGFR values $\leq$ 13 mL/min/1.73 m^2 in this data set.

Safety:

A total of 26 AEs were reported in the study, of these 22 TEAEs were reported by 12 (31.6%) of the 38 subjects. Four AEs were reported prior to study drug administration. One subject (12.5%) from Cohort 1 reported 1 TEAE, 2 subjects (25%) from Cohort 2 reported 2 TEAEs, 4 subjects (50%) from Cohort 3 reported 7 TEAEs, 2 subjects (33.3%) from Cohort 4 reported 3 TEAEs, 3 subjects (37.5%) from Cohort 5 (Period 1) reported 9 TEAEs, and 1 subject (12.5%) from Cohort 5 (Period 2) reported 2 TEAEs. Five subjects (13.2%) experienced 5 causally related TEAEs (ADRs) which were reported for 3 subjects (37.5%) in Cohort 3 and 1 subject (12.5%) each in Cohort 1 and Cohort 5 (Period 1) (Table 4). The casually related TEAEs were nausea, rash maculo-papular, urticaria in Cohort 3, myalgia in Cohort 1, and polyuria in Cohort 5 (Period 1).

No deaths or SAEs were reported in the study. One subject from Cohort 3 had a TEAE of urticaria which led to premature withdrawal from the study and was considered related to study drug. The most frequently reported TEAE was dermatitis contact, reported by 1 subject each in Cohorts 2, 4, and 5 (all assessed as unrelated to study drug). The majority of the TEAEs were mild. All AEs reported resolved.

The incidence of TEAEs did not appear to have any correlation with the degree of renal impairment.

No clinically significant abnormal findings in laboratory evaluations, ECGs and QTc evaluations, or in vital signs were found.

Table 4 Summary of Treatment Emergent Adverse Events (Event Level) by Relationship

System Organ Class	Preferred Term	Related	Unrelated
Cohort 1			
Musculoskeletal And Connective Tissue Disorders	Myalgia	1	
Cohort 2			
Gastrointestinal Disorders	Constipation		1
Skin And Subcutaneous Tissue Disorders	Dermatitis Contact		1

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Cohort 3			
Gastrointestinal Disorders	Nausea	1	
Metabolism And Nutrition Disorders	Gout		1
Musculoskeletal And Connective Tissue Disorders	Flank Pain		1
Nervous System Disorders	Dizziness		1
Skin And Subcutaneous Tissue Disorders	Rash Maculo-papular	1	
	Urticaria	1	
Vascular Disorders	Phlebitis		1
Cohort 4			
Infections And Infestations	Upper Respiratory tract Infection		1
Skin And Subcutaneous Tissue Disorders	Dermatitis Contact		1
Cohort 5 (Period 1)			
Gastrointestinal Disorders	Nausea		1
Injury, Poisoning And Procedural Complications	Postoperative Wound Complication		1
Metabolism And Nutrition Disorders	Hypoglycaemia		1
Nervous System Disorders	Headache		1
	Paraesthesia		1
Renal And Urinary Disorders	Polyuria	1	
Skin And Subcutaneous Tissue Disorders	Dermatitis Contact		1
Vascular Disorders	Flushing		1
Cohort 5 (Period 2)			
Injury, Poisoning And Procedural Complications	Postoperative Wound Complication		1
	Arteriovenous Fistula Site Complication		1

Cohort 1: Matched healthy subjects with normal renal function
Cohort 2: Subjects with mild renal impairment

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Cohort 3: Subjects with moderate renal impairment

Cohort 4: Subjects with severe renal impairment

Cohort 5: Subjects treated by HD

CONCLUSIONS

Pharmacokinetics:

- The CL of S-649266 was significantly affected by renal function, suggesting a need for dose adjustments depending upon the degree of renal function impairment.
- Impairment of renal function was observed to significantly impact S-649266 plasma $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, λ_z, $t_{1/2,z}$, and CL for subjects with moderate renal impairment, severe renal impairment, and subjects treated by HD as compared to subjects with normal renal function.
- Geometric mean ratios of S-649266 $AUC_{0\text{-inf}}$ in subjects with mild, moderate, severe renal impairment, and subjects treated by HD (non-dialysis period) relative to normal renal function were 1.025, 1.464, 2.546 and 4.128, respectively. Geometric mean ratios of S-649266 $AUC_{0\text{-inf}}$ increased with increase in the degree of renal impairment, indicating the increase in exposure with worsening of renal function.
- Geometric mean S-649266 $t_{1/2z}$ was 2.82 hours, 2.98 hours, 4.13 hours, 6.91 hours and 9.60 hours in subjects with normal, mild, moderate, and severe renal impairment and subjects treated by HD (non-dialysis period), respectively.
- The CL_R in subjects with severe renal impairment and subjects treated by HD (non-dialysis period) decreased by 85.1% and 99.6%, respectively, compared to that in subjects with normal renal function. Geometric mean $Feu_{0\text{-}72}$ of S-649266 was 68.6%, 68.3%, 55.5%, 26.0%, and 0.988% in subjects with normal, mild, moderate, severe renal impairment, and subjects treated by HD (non-dialysis period), respectively.
- Mean S-649266 plasma C_{max} and V_{ss} in subjects with any stage of renal impairment did not significantly differ from subjects with normal renal function.
- Hemodialysis removed S-649266 in plasma (Fr) by 62.3% (8.4%) [GM (GM CV%)]. The Fr was comparable to $Feu_{0\text{-}72}$ in subjects with normal renal function, 68.6% (17.3%).
- S-649266 CL values were positively correlated with both subject eGFR and

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CL_{cr}, as demonstrated.

- There was no apparent effect of renal function status on S-649266 plasma protein binding.

Safety:

- This study demonstrated that single IV dose of 1000 mg S-649266 was well tolerated in subjects with varying degrees of renal impairment and in subjects with normal renal function.

Final Report Date: 29 December 2014

CSR Amendment 1: 09 March 2015

CSR Amendment 2: 11 May 2016

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