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Pharmacokinetics of a Single Oral Dose of the MEK1/2 Inhibitor Selumetinib in Subjects With End-Stage Renal Disease or Varying Degrees of Hepatic Impairment Compared With Healthy Subjects

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Abstract

Two phase I open-label studies were conducted to investigate the pharmacokinetics (PK), safety, and tolerability of single oral doses of selumetinib in subjects with end-stage renal disease (ESRD) undergoing hemodialysis and subjects with varying degrees of hepatic impairment; both studies included a matched control group comprised of healthy individuals. In the renal impairment study, subjects received single doses of selumetinib 50 mg; those with ESRD received selumetinib before and after dialysis (with a between-treatment washout period of ≥7 days). In the hepatic impairment study, subjects received varying single doses of selumetinib (20-50 mg) depending on liver dysfunction (mild, moderate, or severe as per Child-Pugh classification). PK, safety, and tolerability data were collected from both studies. Overall, 24 subjects were included in the renal impairment study (ESRD, N = 12; healthy subjects, N = 12). Selumetinib exposure (AUC and C_{max}) was not increased in the ESRD group vs healthy subjects. Selumetinib exposure was lower when selumetinib was dosed before vs after dialysis, although individual exposure was variable. Overall, 32 subjects were included in the hepatic impairment study (mild, moderate, and severe impairment, N = 8 per group; healthy subjects, N = 8). Generally, dose-normalized total selumetinib exposure was increased by 25% to 59% in subjects with moderate and severe hepatic impairment compared with healthy subjects. Increasing Child-Pugh score, decreasing serum albumin, and increasing prothrombin time correlated with increasing unbound selumetinib exposure. In both studies, selumetinib was well tolerated with no new safety concerns. These studies will inform dose adjustment considerations in patients.

Keywords

selumetinib, pharmacokinetics, end-stage renal disease, hepatic impairment, hemodialysis

Selumetinib (AZD6244, ARRY-142886) is an oral, potent, and selective allosteric MEK1/2 inhibitor[1] with a short half-life[2,3] and has been demonstrated to exhibit linear pharmacokinetics up to 75 mg in healthy volunteers.[2] Selumetinib can undergo oxidative metabolism through CYP enzymes.[6] The main active metabolite, N-desmethyl selumetinib, shows a 3- to 5-fold greater potency for MEK1 inhibition than the parent compound in vitro, but lower exposure, with AUC and C_{max} typically ~7% of the parent compound[4,5] (NCT02093728 and NCT02046850). Another metabolite, selumetinib amide, is up to 50-fold less active than selumetinib.[4] Selumetinib is predominantly excreted in feces, with very little being eliminated unchanged in urine (NCT01931761).[6]

Selumetinib is currently in clinical development for the treatment of a variety of solid tumors. Selumetinib monotherapy produced a clinically meaningful increase in iodine uptake and retention in patients with radioiodine-refractory differentiated thyroid cancer.[7] The clinical efficacy, safety, and tolerability of selumetinib in combination with radioactive iodine therapy in patients with differentiated thyroid cancer are currently being investigated in a phase III randomized, placebo-controlled study (NCT01843062).[8] This ongoing phase III trial of selumetinib utilizes a dose

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of 75 mg twice daily administered in the fasted state (NCT01843062).[8] Last, selumetinib monotherapy has shown a decrease in plexiform neurofibroma (PN) volume in pediatric patients with neurofibromatosis type 1 and inoperable PNs, and a phase II registration trial is currently underway (NCT01362803).[9]

It is likely that some patients who would receive selumetinib could have existing comorbidities that may include hepatic or renal impairment and that could impact on an individual's ability to metabolize and excrete drugs, potentially resulting in increased drug exposure and toxicity. Consequently, it is important to establish the impact of such organ impairment on selumetinib exposure to establish whether dose adjustments are required. In terms of selumetinib, this may be particularly relevant for patients with hepatic impairment given that the drug is metabolized by hepatic CYP enzymes. Furthermore, although little selumetinib is excreted in the urine, this may not be the case for its metabolites. For this reason, studies that quantify the impact of renal and hepatic impairment on the pharmacokinetics (PK) of selumetinib and its metabolites are warranted and are a regulatory requirement. Data from such studies may be used to determine the appropriate dose of selumetinib in patients with renal or hepatic impairment and to inform labeling statements with regard to posology.

The current manuscript describes 2 phase I trials that compare the exposure of selumetinib and N-desmethyl selumetinib following single oral doses of selumetinib in subjects with dialysis-dependent end-stage renal disease (ESRD) or varying degrees of hepatic impairment. Both studies included a matched control group comprising healthy male and female subjects known to be free from any significant illness. Because selumetinib is being developed in adults with cancer, there are limited safety data in healthy subjects; consequently, it is considered that any dosing in healthy subjects does not exceed the mean steady-state exposure observed in non-Asian patients in whom a dose of 75 mg twice daily is well tolerated, with mean exposure to remain below 1307 ng/mL for maximum observed concentration in plasma (C_{max}) and/or 4736 ng·h/mL for area under the plasma concentration-time curve from 0 to 12 hours postdose ($AUC_{(0\text{-}12)}$).[2] To avoid the potential of exceeding the predefined exposure limits in subjects with hepatic or renal impairment, the selumetinib doses used in these studies were lower than the maximum dose of 75 mg permitted in healthy subjects.

Methods

Study Conduct

Two phase I studies were conducted to determine the PK, safety, and tolerability of selumetinib in healthy subjects and in subjects with either renal or hepatic impairment; both studies, along with the study protocols (including any amendments), were approved by Aspire Institutional Review Board (Santee, California). The studies were conducted at the Orlando Clinical Research Center (Orlando, Florida) and were performed in accordance with the ethical principles originating from the Declaration of Helsinki that are consistent with the International Conference on Harmonisation–Good Clinical Practice. Subjects in both studies provided signed and dated written informed consent.

Trial Design

Renal Impairment Study. This was an open-label study (NCT02063204) that, as per the protocol and draft guidance from the United States Food and Drug Administration (FDA),[10] was to be conducted in 2 stages. The first stage of the study involved a comparison of the selumetinib PK and unbound selumetinib concentrations following a single oral dose of selumetinib 50 mg in subjects with ESRD requiring dialysis and in healthy subjects (primary objective). Subjects with ESRD received a single dose of selumetinib after and before dialysis (with a washout period of at least 7 days between doses). The rationale for including subjects with ESRD in the first stage of the study was to include "worst case" subjects who had little or no renal function and in whom increased drug exposure (if applicable) would be the most apparent. The second stage of the study was to compare the PK of selumetinib in subjects with all intermediate levels of renal impairment—mild, moderate, and severe renal impairment—however, this was only to be conducted if the difference in mean selumetinib exposure in the ESRD group was greater than 1.5-fold compared to the healthy subjects.

Secondary objectives of the study included an assessment of the safety and tolerability of selumetinib and characterization of the PK of selumetinib metabolites in subjects with ESRD compared with healthy subjects.

Hepatic Impairment Study. The primary objective of this open-label study (NCT02063230) was to characterize the selumetinib PK and unbound selumetinib concentrations following a single oral dose of selumetinib in healthy subjects with normal liver function and in subjects with varying degrees of hepatic impairment, as defined by the Child-Pugh classification. The planned doses of selumetinib in subjects with mild, moderate, and severe hepatic impairment were 50 mg, 50 mg, and 25 mg, respectively. To ensure that the exposure limit was not exceeded, dosing of the different subject groups (mild, moderate, or severe impairment) was staggered, and the dose for patients with moderate or severe hepatic impairment was selected based on interim exposure and safety data from the preceding group

(eg, data from patients with mild hepatic impairment was used to guide dose in patients with moderate hepatic impairment). Secondary objectives included an assessment of the safety and tolerability of selumetinib and characterization of the PK of selumetinib metabolites in subjects with hepatic impairment compared with healthy subjects.

Subject Selection

In both studies, males and females (of nonchildbearing potential) were eligible to participate. All subjects were required to be aged ≥18 years, have a body weight of ≥50 kg (renal impairment study) or ≥45 kg (hepatic impairment study), and a body mass index (BMI) of 18 to 40 kg/m^2. Key exclusion criteria in both studies were as follows: Japanese or non-Japanese Asian ethnicity, or 1 parent or grandparent of Japanese or non-Japanese Asian ethnicity; previous administration of selumetinib or treatment with another new chemical entity in the 30 days preceding the first dose of selumetinib; and treatment with any medication known to have moderate/strong inhibitory or inducer effects on CYP3A in the 30 days preceding the first dose of selumetinib and until follow-up.

Renal Impairment Study. Subjects were only recruited to the first stage of the study because data from this stage indicated that the second stage was not required. For the first stage, healthy subjects were required to have an estimated creatinine clearance (CrCL) of >80 mL/min using the Cockcroft-Gault formula and could not have any clinically significant disease or disorder for which participation in the study might put them at risk or that might influence the results of the study. No specific CrCL was specified in subjects with ESRD, but all had to be undergoing hemodialysis and had to have stable renal function for ≥3 months. Subjects with ESRD could include individuals who had undergone a renal transplant and who were receiving hemodialysis due to transplant failure. ESRD subjects were excluded from participating if they had implemented significant changes in the dose of any medically required medications in the 2-week period preceding the prestudy examination or had received prescribed additions to their routine medication and/or had used any disallowed comedications in the 3 weeks prior to admission to the study center. ESRD subjects with unstable or uncompensated hepatic disease were also excluded from participating in the study.

Healthy subjects were recruited after the inclusion of two thirds of all ESRD subjects and were matched to ESRD subjects according to sex, age, and BMI.

Hepatic Impairment Study. All subjects were required to have a calculated CrCL of >50 mL/min using the Cockcroft-Gault formula. Subjects with hepatic impairment had to have liver cirrhosis and hepatic impairment for ≥3 months prior to initiation of the study. Healthy subjects had to be in good health and have negative results for serum hepatitis B surface antigen and hepatitis C antibody. Healthy subjects were only recruited after the recruitment of approximately three quarters of all subjects with hepatic impairment stratified as Child-Pugh A, B, and C (Supplemental Table S1); healthy subjects were matched to subjects with hepatic impairment according to sex, age, and BMI. The laboratory tests and related exclusion criteria used are described in Supplemental Tables S2 and S3.

Study Treatment

Renal Impairment Study. Following a screening period of 28 days, eligible subjects received treatment with selumetinib (visit 1). Treatment was administered in a fasted state: subjects fasted for 2 hours prior to selumetinib administration and remained fasted until 4 hours postdose. No water was allowed during this period except for 240 mL (where required) to aid in the administration of treatment.

Subjects with ESRD participated in 2 treatment periods to assess selumetinib exposure under both nondialysis and dialysis conditions. In treatment period 1, subjects received a single oral dose of selumetinib 50 mg (2×25 mg capsules) on day 1 of visit 2, following completion of dialysis. Subjects remained at the study center for PK sampling until the start of their next dialysis session (72 hours postdose). In treatment period 2, following a washout period of ≥7 days, subjects received a second single oral dose of selumetinib 50 mg (2×25 mg capsules) on day 1 of visit 3; treatment was administered 1 hour prior to the start of dialysis, and subjects remained at the study center until completion of study assessments on day 4 of treatment period 2. Subjects returned to the study center 3 to 7 days after discharge for follow-up (visit 4) (Figure 1A).

Healthy subjects participated in 1 treatment period, which involved the administration of a single oral dose of selumetinib 50 mg (2×25 mg capsules) on day 1 of visit 2. Subjects returned to the study center after 3 to 7 days for follow-up (visit 3) (Figure 1A).

Subjects with ESRD were administered a 50 mg dose of selumetinib, which is lower than the maximum dose of 75 mg permitted in healthy subjects. Although renal impairment was not expected to increase exposure to selumetinib, a lower selumetinib dose was selected as a precaution against any potential for increased exposure. Healthy subjects also received a 50 mg dose to match the dose used in subjects with renal impairment.

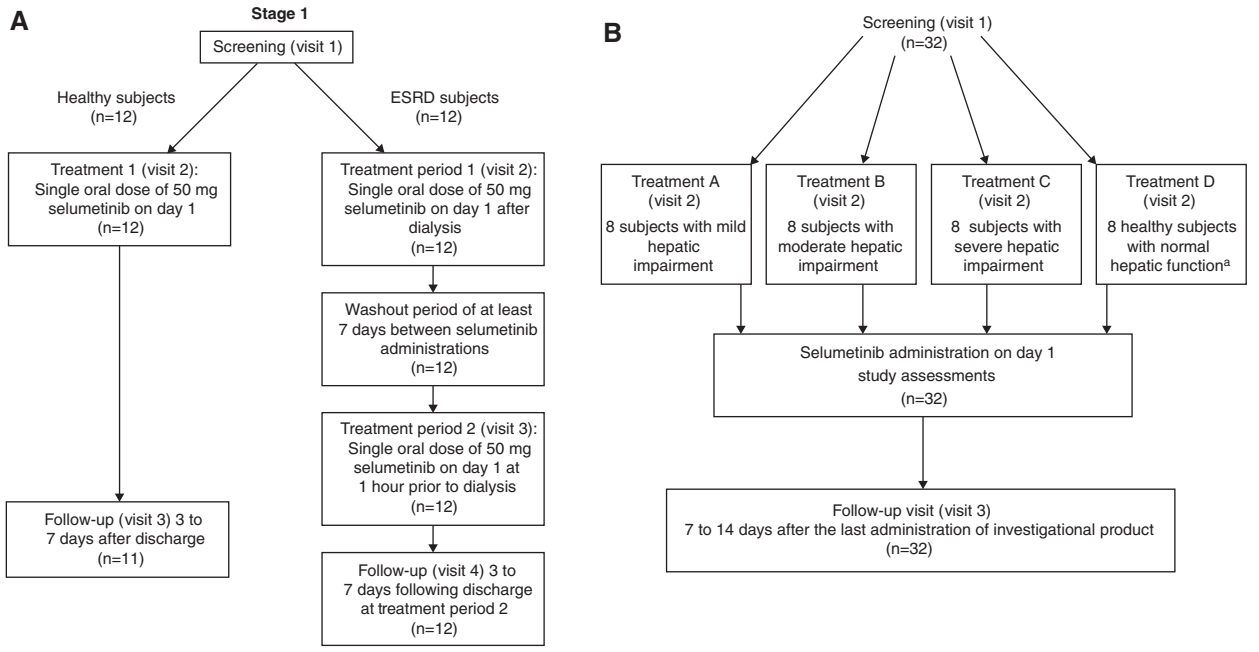

Figure 1. Design of (A) the renal impairment study (stage 1 only) and (B) the hepatic impairment study. ESRD, end-stage renal disease. [a]Healthy subjects were only recruited after the recruitment of approximately three quarters of all subjects with hepatic impairment.

Hepatic Impairment Study. Following a screening period of 28 days, subjects received a single oral dose of selumetinib on day 1 of visit 2 (Figure 1B). Subjects received treatment in the morning following an overnight fast and remained fasted until 4 hours postdose. No fluids were allowed in the period from 1 hour before to 1 hour following the administration of selumetinib, except for 240 mL of water to aid in the administration of treatment. Subjects were discharged on completion of all study procedures on day 6 and returned to the study center 7 to 14 days postdose for follow-up (visit 3) (Figure 1B).

The planned dose of selumetinib in subjects with hepatic impairment depended on the degree of hepatic impairment (according to Child-Pugh criteria): subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) impairment were to receive selumetinib 50 mg, 50 mg, and 25 mg, respectively. Treatment was administered in a partially sequential manner to determine (1) if dose reductions were necessary in subjects with the same degree of hepatic impairment and (2) if reductions in the starting dose in subjects with a greater degree of hepatic impairment were necessary. Specifically, once 4 or more subjects with mild hepatic impairment had received treatment, the safety, tolerability, and plasma PK data from these subjects were assessed by the study Safety Review Committee (SRC) before subjects with moderate hepatic impairment were recruited. Similarly, once 4 or more subjects with moderate hepatic impairment had received treatment, the safety, tolerability, and PK data from all subjects dosed up until that point were assessed by the SRC before subjects with severe hepatic impairment were recruited.

The selumetinib dose administered to subjects with liver impairment was lower than the maximum dose permitted in healthy subjects (ie, 75 mg) to anticipate any increased selumetinib exposure in these subjects and to ensure they did not exceed predefined exposure limits, as previously described. A 50 mg dose was administered to healthy subjects to match the planned dose in subjects with mild and moderate hepatic impairment.

Pharmacokinetic Assessments

PK parameters were determined using standard noncompartmental methods with Phoenix® WinNonlin® Version 6.3 or higher (Pharsight Corp, Mountain View, California) or SAS® Version 9.2 or higher (SAS Institute, Inc, Cary, North Carolina).

In the renal impairment study, serial blood samples to measure plasma concentrations of selumetinib and N-desmethyl selumetinib were collected predose (0 hours) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 18, 24, 36, 48, and 72 hours postdose. In the hepatic impairment study the same sampling time points were applied, with the exception of no sampling at 5 and 18 hours and additional sampling at 96 and 120 hours. In both studies plasma concentrations of the selumetinib amide metabolite were measured; however, they were largely

below the lower limit of quantification (2 ng/mL) of the assay and are not reported here.

Plasma samples were used to determine the unbound fraction because this reflects the fraction that exhibits pharmacologic effects. Initially samples at 1, 6, and 24 hours were selected for analysis from the full profile available. However, results from the initial analyses at these time points showed that the unbound fractions at 6 and 24 hours were not detectable due to the low unbound fraction. Therefore, samples taken at the time points showing the highest 3 plasma concentrations of selumetinib for each subject from the plasma analysis were analyzed. The mean percentage unbound fraction from the 3 results within a subject was then applied to all samples from this subject. Unbound fraction was evaluated using the plasma ultrafiltrate method.[11]

In the renal impairment study, blood dialysate was originally planned to be collected over 1-hour intervals in custom buckets. However, to minimize the dilution of analytes in the sample, dialysate spot samples were collected every 30 minutes during dialysis, and PK parameters were determined using the area under the excretion rate curve method.

In the renal impairment study, urine was collected at –12 to 0 (predose) and 0 to 6, 6 to 12, 12 to 24, 24 to 36, 36 to 48, and 48 to 72 hours, whereas in the hepatic impairment study, urine was collected at intervals from –12 to 0 (predose) and 0 to 6, 6 to 12, 12 to 24, 24 to 36, 36 to 48 hours, and every 24 hours thereafter up to 120 hours.

Bioanalysis Methods

Sensitive LC-MS/MS assays were developed and validated that demonstrated acceptable precision, accuracy, and selectivity for selumetinib and its metabolites in the appropriate matrices.[11] They were validated based on FDA and European Medicines Agency guidance[12–14] and on laboratory standard operating procedures. The mass spectrometer used was an API 5000 or 5500 triple quadruple mass spectrometer (AB Sciex, Foster City, California). This was run in positive electrospray, multiple reaction monitoring, with an ionspray voltage of 5500 V and TurboIonSpray temperature of 600°C. In plasma, the following typical transitions were monitored for the analytes: selumetinib 459.0/397.2; N-desmethyl sel 445.3/383.1; sel-amide 339.4/301.3. For the urine and dialysate, the following transitions were used: sel 459.2/206.2; N-desmethyl sel 445.2/ 287.2. For plasma ultrafiltrate, the following transitions were used: sel 459.2/ 301.2 and N-desmethyl sel 445.2/ 307.2. These analyses used stable label carbon-13 internal standards, and the mass spectrometer conditions were typically equivalent to the unlabeled compound except that the dwell time was 75 milliseconds for the analytes and 50 milliseconds for the internal standards, and the equivalent carbon-13 transitions were analyzed. The validated ranges of the methods for selumetinib and N-desmethyl sel were 2.00 to 2000 ng/mL and 2.00 to 500 ng/mL, respectively, in plasma; 10.0 to 10,000 ng/mL and 2.00 to 2500 ng/mL in urine; 1.00 to 1000 ng/mL, and 0.200 to 250 ng/mL in blood dialysate; and 0.500 to 250 ng/mL and 0.500 to 250 ng/mL in plasma ultrafiltrate.

Safety and Tolerability

Adverse events (AEs) were collected for all subjects across both studies from screening until the follow-up visit and were classified by System Organ Class and preferred term using the Medical Dictionary for Regulatory Activities Version 17.0. Data relating to vital signs, electrocardiograms (ECGs), and clinical laboratory tests were also recorded.

Statistical Analysis

Statistical analyses for both studies were performed by Quintiles (Durham, North Carolina) as per the company's standard operating procedures using SAS® Version 9.4 and additional validated software as appropriate.

Renal Impairment Study. It was considered that a minimum of 8 evaluable subjects in each group would provide adequate information to assess the effects of renal impairment on the PK of selumetinib, while exposing as few subjects as possible to the study drug and procedures. Although no formal sample size calculations were performed, natural log C_{max} data from a study investigating the relative bioavailability of different capsule formulations of selumetinib (NCT01635023) indicated that a minimum of 8 evaluable subjects from each group would provide an 80% chance that the 1-sided 95% confidence interval (CI) would exclude the possibility of a doubling in C_{max}, assuming a geometric coefficient of variation of 40.4% and an expected ratio of 120%.

Log-transformed PK parameters for selumetinib and N-desmethyl selumetinib were analyzed using a linear fixed-effect analysis of variance (ANOVA) model, with renal impairment group as a fixed effect (ie, subjects with ESRD dosed postdialysis vs healthy subjects). To assess potential differences between the 2 treatment periods in subjects with ESRD, PK parameters for selumetinib and N-desmethyl selumetinib were also analyzed using a repeated-measures ANOVA model on the log-transformed data, with the model including treatment period as a repeated fixed effect (ie, dosed postdialysis [treatment period 1] vs on dialysis [treatment period 2]). Geometric least-squares (LS) means and ratios (with 2-sided 90%CIs) were estimated.

Hepatic Impairment Study. It was considered that 8 subjects per group would be adequate to provide suitable information on the primary objective, while exposing as few subjects as possible to study procedures. Although no formal sample size calculations were performed, the number of subjects included was in line with FDA guidance on evaluating PK outcomes in subjects with hepatic impairment.[15]

Dose-normalized PK parameters were logarithmically transformed using natural logarithms and analyzed using an ANOVA model with a factor fitted for hepatic impairment status (mild, moderate, severe, or normal). Geometric LS means for each hepatic group were estimated. In addition, geometric LS ratios (with 2-sided 90%CIs) for each level of hepatic impairment were compared to that of healthy subjects. Log-transformed dose-normalized PK parameters were also analyzed using regression models with serum albumin, prothrombin time, and Child-Pugh score included as separate independent variables; healthy subjects with normal hepatic function were included in all of these analyses except for Child-Pugh score analyses.

Results

Subject demographics are shown in Table 1. In the renal impairment study, subjects had a mean age of 50 years and a mean BMI of 27.6 kg/m^2. Corresponding values in the hepatic impairment study were 56 years and 27.6 kg/m^2, respectively. The majority of subjects in both studies were male.

Pharmacokinetics

Renal Impairment Study: First Stage. Overall, 24 subjects were enrolled (ESRD, N = 12; healthy subjects, N = 12), and all received treatment (Supplemental Figure S1). Twenty-three subjects (95.8%) completed the study; 1 healthy subject withdrew consent after receiving selumetinib (on day 3).

Total selumetinib exposure (AUC and C_{max}) was lower in the ESRD group than in healthy subjects (Figure 2). Additionally, within the ESRD group, total selumetinib exposure was lower when selumetinib was dosed before dialysis than when dosed after dialysis (Figure 2 and Supplemental Table S1). Selumetinib AUC and C_{max} were 17% and 30% lower, respectively, when selumetinib was dosed before vs after dialysis. N-Desmethyl selumetinib AUC and C_{max} were 10% and 15% lower, respectively, when selumetinib was dosed before vs after dialysis (Supplemental Table S4).

Key PK parameters of selumetinib and N-desmethyl selumetinib following each treatment are shown in Table 2. Healthy subjects and those with ESRD had a similar median selumetinib time to C_{max} (t_{max}). Mean terminal half-life ($t_{1/2}$) was also similar in healthy and ESRD subjects. Table 3 shows that selumetinib AUC was 28% lower in the ESRD group (dosed post dialysis) vs healthy subjects. For the other parameters,

Table 1. Baseline and Demographic Characteristics of Subjects Included in the Renal and Hepatic Impairment Studies

Renal Impairment Study	ESRD[a] (N = 12)	Healthy[b] (N = 12)	All Subjects (N = 24)
Age, years	48 ± 7	51 ± 5	50 ± 6
Male sex, N (%)	10 (83.3)	10 (83.3)	20 (83.3)
BMI, kg/m^2	28.1 ± 4.9	27.1 ± 1.5	27.6 ± 3.6
Race/ethnicity, N (%)			
White	1 (8.3)	7 (58.3)	8 (33.3)
Black	11 (91.7)	5 (41.7)	16 (66.7)

Hepatic Impairment Study	Mild[c] (N = 8)	Moderate[d] 50 mg (N = 6)	Moderate[d] All (N = 8)	Severe[e] (N = 8)	Healthy (N = 8)	All Subjects (N = 32)
Age, years	55 ± 4	56 ± 5	57 ± 5	55 ± 9	57 ± 7	56 ± 6
Male sex, N (%)	7 (87.5)	3 (50.0)	5 (62.5)	6 (75.0)	5 (62.5)	23 (71.9)
BMI, kg/m^2	26.8 ± 5.2	26.4 ± 4.8	27.1 ± 4.2	28.3 ± 5.0	28.2 ± 2.9	27.6 ± 4.3
Race/ethnicity, N (%)						
White	6 (75.0)	4 (66.7)	6 (75.0)	6 (75.0)	6 (75.0)	24 (75.0)
Black	1 (12.5)	2 (33.3)	2 (25.0)	1 (12.5)	2 (25.0)	6 (18.8)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (3.1)
East Indian	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)

Data shown as mean ± standard deviation unless otherwise stated. BMI, body mass index; ESRD, end-stage renal disease.

[a]Requiring hemodialysis.

[b]Creatinine clearance >80 mL/min.

[c]Child-Pugh class A.

[d]Child-Pugh class B (single oral dose of selumetinib 50 mg [N = 6] or selumetinib 25 mg [N = 2]).

[e]Child-Pugh class C.

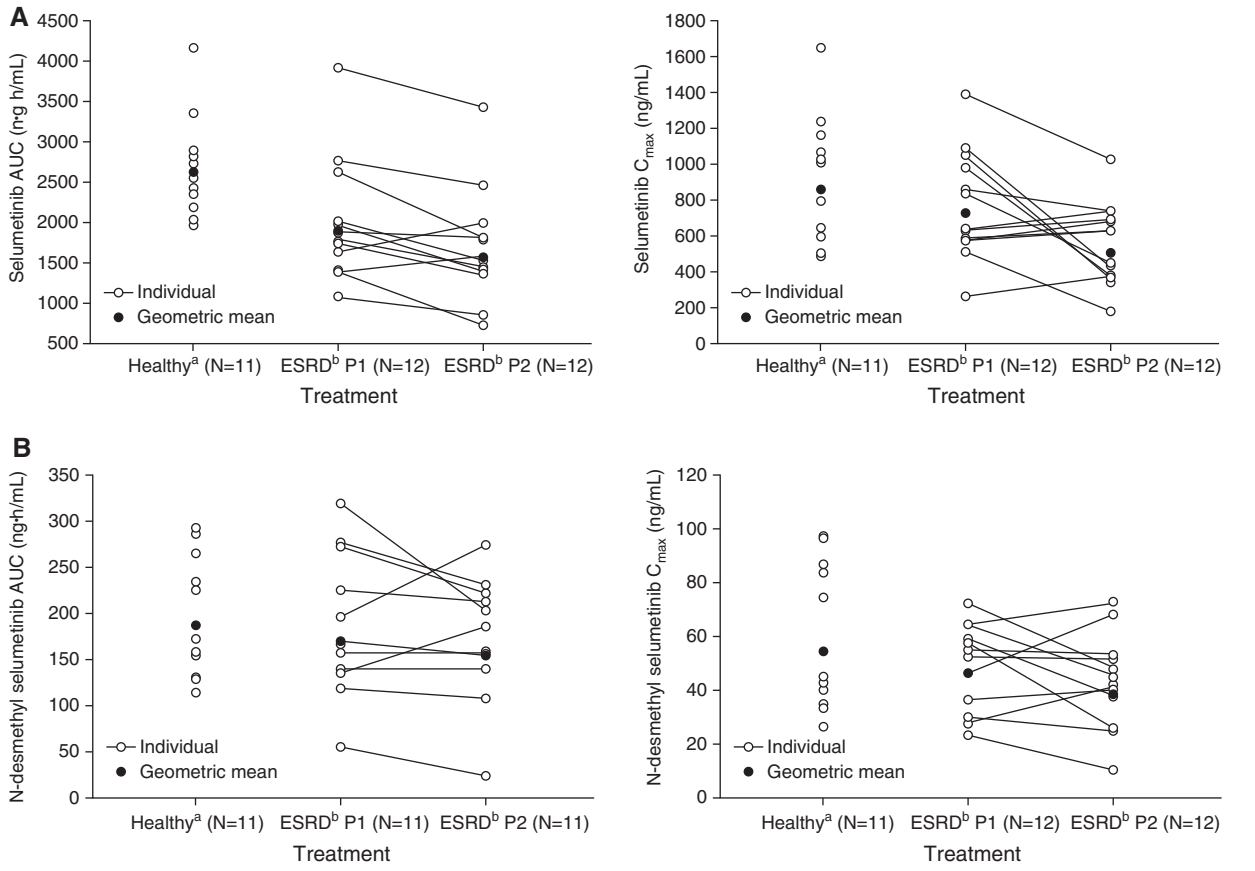

Figure 2. Individual and geometric mean AUC and Cmax for (A) selumetinib and (B) N-desmethyl selumetinib according to renal group (healthy[a] or ESRD[b]) and treatment period (P1 vs P2). [a]Creatinine clearance >80 mL/min (single oral dose of selumetinib 50 mg on day 1). [b]Requiring hemodialysis (treatment period 1, single oral dose of selumetinib 50 mg on day 1 after completion of a dialysis session; treatment period 2, single oral dose of selumetinib 50 mg 1 hour before the start of a dialysis session). AUC, area under the plasma concentration-time curve from time 0 to infinity; Cmax, maximum observed plasma concentration; ESRD, end-stage renal disease; P1, treatment period 1 (ie, after dialysis); P2, treatment period 2 (ie, before dialysis).

the difference between ESRD and healthy subjects was <20% (Table 3).

The median unbound fraction (fu,av) of selumetinib determined after a single 50 mg dose of selumetinib to healthy subjects was 0.40% (range 0.33% to 0.46%). Unbound levels of selumetinib were increased in ESRD subjects by approximately 40% (median 0.56%; range 0.30% to 1.26%) compared to healthy subjects (Table 2). The percentage of unbound selumetinib did not appear to be concentration or time dependent (Supplemental Figure S2). Unbound N-desmethyl selumetinib was largely below the limit of quantification of the assay; from the limited samples that were quantifiable, there was generally a slightly higher percentage of unbound N-desmethyl selumetinib in subjects with ESRD vs healthy subjects (Table 2).

In healthy subjects, selumetinib and N-desmethyl selumetinib were minimally excreted in urine, with 0.49% and 0.73% excreted, respectively. Nine of 12 subjects with ESRD did not produce urine; for those who did, the fraction of excreted selumetinib and N-desmethyl selumetinib was lower than that in healthy subjects, at 0.086% to 0.10% and 0.026% to 0.30%, respectively. Negligible concentrations of selumetinib and N-desmethyl selumetinib were cleared by dialysis, with 0.92% and 0.089% of the dose excreted in dialysate, respectively.

Renal Impairment Study: Second Stage. The second stage of the study was not conducted because the mean AUC in the ESRD group was not greater than 1.5-fold compared to that in the healthy subjects.

Hepatic Impairment Study. Overall, 32 subjects were enrolled and received treatment; all completed the study (Supplemental Figure S1). All subjects in the mild impairment group received selumetinib 50 mg. Six subjects in the moderate impairment group received selumetinib 50 mg, as planned; however, interim PK data presented at the SRC meeting showed the group mean C_{max} exceeded the predefined exposure limit, and so the remaining 2

Table 2. Selumetinib and N-Desmethyl Selumetinib Pharmacokinetic Parameters in Subjects With End-Stage Renal Disease (ESRD) and Healthy Subjects

	ESRD[b]		
Parameter[a]	Treatment Period 1 (N = 12) Selumetinib 50 mg	Treatment Period 2 (N = 12) Selumetinib 50 mg	Healthy[c] (N = 11) Selumetinib 50 mg
Selumetinib			
AUC (ng·h/mL)	1880 (35.9)	1560 (44.2)	2620 (22.3)
AUC_u (ng·h/mL)	10.3 (20.1)	N/A	10.6 (23.0)
C_{max} (ng/mL)	725 (45.8)	507 (50.2)	863 (41.5)
$C_{max,u}$ (ng/mL)	3.95 (34.7)	N/A	3.48 (42.5)
t_{max} (h), median (min-max)	1.00 (0.50-2.50)	1.50 (0.50-2.00)	1.50 (1.00-2.50)
$t_{1/2}$ (h), arithmetic mean (SD)	6.55 (1.78)	5.81 (2.09)	7.34 (2.90)
CL/F (L/h)	26.6 (36.0)	32.2 (44.2)	19.1 (22.3)
fu,av (%), median (min-max)	0.556 (0.304-1.26)	N/A	0.400 (0.330-0.456)
N-desmethyl selumetinib			
AUC (ng·h/mL)	171 (50.9)[d]	153 (71.5)[d]	186 (35.0)
AUC_u (ng·h/mL)	2.10 (19.2)[e]	N/A	1.72 (14.4)[e]
C_{max} (ng/mL)	45.1 (40.4)	38.5 (57.7)	53.4 (52.1)
$C_{max,u}$ (ng/mL)	0.561 (14.8)[e]	N/A	0.619 (8.5)[e]
t_{max} (h), median (min-max)	1.25 (0.50-3.00)	1.50 (1.00-2.00)	1.50 (1.00-3.00)
$t_{1/2}$ (h), arithmetic mean (SD)	6.28 (2.87)[d]	5.79 (2.52)[d]	5.41 (1.40)
MR_{AUC}	0.0864 (45.9)[d]	0.0930 (48.6)[d]	0.0710 (38.4)
MR_{Cmax}	0.0623 (42.8)	0.0759 (35.9)	0.0619 (32.9)
fu,av (%), median (min-max)	0.894 (0.710-1.08)[e]	N/A	0.688 (0.659-0.712)[e]

AUC, area under the plasma concentration-time curve from time 0 to infinity; AUC_u, unbound area under the plasma concentration-time curve from time 0 to infinity; C_{max}, maximum observed plasma concentration; $C_{max,u}$, unbound maximum observed plasma concentration; CL/F, apparent oral plasma clearance; fu,av, average fraction unbound; max, maximum; min, minimum; MR_{AUC}, metabolite-to-parent AUC ratio; MR_{Cmax}, metabolite-to-parent C_{max} ratio; N/A, not applicable; SD, standard deviation; t_{max}, time to C_{max}; $t_{1/2}$, terminal half-life.

[a]Data shown as geometric mean (geometric coefficient of variation [%]) unless otherwise stated.

[b]Requiring hemodialysis (treatment period 1, single oral dose of selumetinib 50 mg on day 1 after completion of a dialysis session; treatment period 2, single oral dose of selumetinib 50 mg 1 hour before the start of a dialysis session).

[c]Creatinine clearance >80 mL/min (single oral dose of selumetinib 50 mg on day 1).

[d]N = 11.

[e]N = 4.

Table 3. Comparison of Key Selumetinib and N-Desmethyl Selumetinib Pharmacokinetic Exposure Parameters According to Renal Group (ESRD[a] or Healthy[b])

Parameter	ESRD	Healthy	ESRD/Healthy Ratio (%) (90%CI)
Selumetinib			
AUC (ng·h/mL)	1881	2617	71.89 (58.20, 88.79)
AUC_u (ng·h/mL)	10.25	10.55	97.13 (83.36, 113.17)
C_{max} (ng/mL)	724.6	863.4	83.92 (62.12, 113.37)
$C_{max,u}$ (ng/mL)	3.95	3.48	113.23 (86.66, 147.95)
N-desmethyl selumetinib			
AUC (ng·h/mL)	171.0	185.9	91.95 (67.73, 124.83)
C_{max} (ng/mL)	45.15	53.45	84.48 (61.60, 115.86)

Data presented as geometric least-squares means. Results based on linear fixed-effect analysis of variance model using the logarithm of AUC and C_{max} as the response variable and renal impairment group as a fixed effect. AUC, area under the plasma concentration-time curve from time 0 to infinity; AUCu, unbound area under the plasma concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; $C_{max,u}$, unbound maximum observed plasma concentration; ESRD, end-stage renal disease.

[a]Requiring hemodialysis (treatment period 1, single oral dose of selumetinib 50 mg on day 1 after completion of a dialysis session) (N = 12 for all parameters with the exception of N = 11 for N-desmethyl selumetinib AUC).

[b]Creatinine clearance >80 mL/min (single oral dose of selumetinib 50 mg on day 1) (N = 11).

subjects in the moderate impairment group received selumetinib 25 mg. The data from these 2 moderate hepatic impairment subjects were not included in plasma concentration or PK parameter summaries except where the data had been dose normalized. All subjects in the severe impairment group received a lower selumetinib dose of 20 mg than initially planned as a result of the interim PK data from the moderate impairment group. The 2 moderate hepatic impairment subjects who received selumetinib 25 mg were not

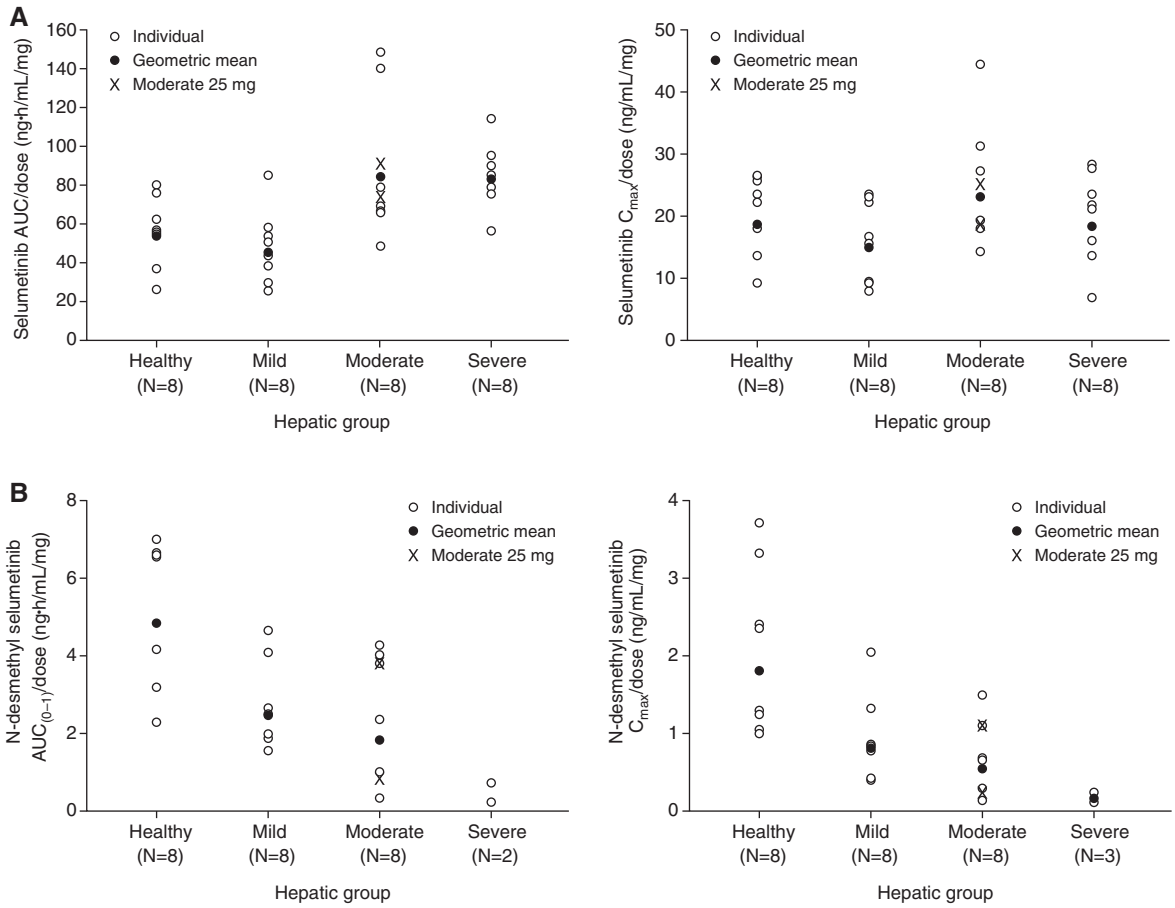

Figure 3. Individual and geometric mean AUC/dose or $AUC_{(0\text{-}t)}$/dose and C_{max}/dose for (A) selumetinib and (B) N-desmethyl selumetinib according to hepatic group: mild, Child-Pugh class A (single oral dose of selumetinib 50 mg); moderate, Child-Pugh class B (single oral dose of selumetinib 50 mg [N = 6] or selumetinib 25 mg [N = 2]); severe, Child-Pugh class C (single oral dose of selumetinib 20 mg); healthy, single oral dose of selumetinib 50 mg. AUC/dose, area under the plasma concentration-time curve from time 0 to infinity divided by dose; $AUC_{(0\text{-}t)}$/dose, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration divided by dose; C_{max}/dose, maximum observed plasma concentration divided by dose.

included in plasma concentration or PK parameter summaries except where the data had been dose normalized.

Scatter plots depicting individual and the geometric mean of dose-normalized total selumetinib and N-desmethyl selumetinib exposure by hepatic group are presented in Figures 3A and 3B, respectively. Selumetinib and N-desmethyl selumetinib PK parameters are summarized in Table 4. Median selumetinib t_{max} was similar in healthy subjects and in subjects with hepatic impairment. Mean $t_{1/2}$ was also similar across the groups. Geometric mean apparent oral clearance (CL/F) was similar in healthy subjects and in subjects with mild impairment but lower in subjects with moderate and severe hepatic impairment. Median N-desmethyl selumetinib t_{max} was similar between the subject groups; mean $t_{1/2}$ was lower in subjects with mild or moderate hepatic impairment than in healthy subjects. N-Desmethyl selumetinib concentrations were largely below the limit of quantification of the assay for subjects with severe impairment; hence, limited PK parameters are reported for this group.

Compared with healthy subjects, dose-normalized total selumetinib exposure was, on average, lower in subjects with mild hepatic impairment (Table 5). Dose-normalized AUC (AUC/dose) was 14% lower, and C_{max}/dose was 22% lower, on average. Dose-normalized total selumetinib exposure was typically higher in subjects with moderate or severe hepatic impairment, compared with healthy subjects, with the exception of the severe impairment group C_{max}/dose, which was similar. In the moderate and severe impairment groups, AUC/dose was 59% and 57% higher, respectively; C_{max}/dose was 25% higher in the moderate impairment group.

The median unbound fraction (fu,av) of selumetinib determined after a single 50 mg dose of

Table 4. Selumetinib and N-Desmethyl Selumetinib Pharmacokinetic Parameters in Subjects With Mild,[a] Moderate,[b] or Severe[c] Hepatic Impairment and Healthy Subjects[d]

	Hepatic impairment			
Parameter[e]	Mild (N = 8) Selumetinib 50 mg	Moderate (N = 8) Selumetinib 50 mg (N = 6) or 25 mg (N = 2)	Severe (N = 8) Selumetinib 20 mg	Healthy (N = 8) Selumetinib 50 mg
Selumetinib				
AUC/dose (ng·h/mL/mg)	45.9 (39.0)	85.1 (38.3)	84.3 (20.1)	53.6 (37.3)
C_{max}/dose (ng/mL/mg)	14.8 (47.0)	23.6 (37.4)	18.5 (49.9)	18.9 (37.0)
t_{max} (h), median (min-max)	1.25 (0.50-4.00)	1.00 (1.00-1.00)[f]	1.00 (0.50-2.00)	1.00 (1.00-1.50)
$t_{1/2}$ (h), arithmetic mean (SD)	7.72 (2.28)	9.92 (2.63)[f]	9.02 (1.28)	8.02 (1.94)
CL/F (L/h)	21.8 (38.9)	11.7 (45.5)[f]	11.9 (19.9)	18.6 (37.3)
fu,av (%), median (min-max)	0.28 (0.23-0.34)	0.30 (0.22-0.42)[e]	0.65 (0.46-1.19)	0.35 (0.28-0.45)
N-desmethyl selumetinib				
$AUC_{(0-t)}$/dose (ng·h/mL/mg)	2.45 (41.1)	1.83 (129.6)	ND[g]	4.84 (43.4)
C_{max}/dose (ng/mL/mg)	0.804 (57.7)	0.548 (102.8)	0.173 (44.3)	1.81 (57.0)
t_{max} (h), median (min-max)	1.50 (1.00-4.00)	1.25 (1.00-1.50)[f]	2.00 (1.50-2.00)[h]	1.00 (1.00-2.00)
$t_{1/2}$ (h), arithmetic mean (SD)	5.18 (1.51)[f]	7.72 (2.92)[i]	N/A	9.24 (3.33)
$MR_{AUC(0-t)}$	0.0542 (58.9)	0.0221 (158.5)[f]	ND[g]	0.0930 (43.6)
MR_{Cmax}	0.0543 (61.6)	0.0229 (140.1)[f]	0.00778 (29.2)[h]	0.0957 (43.6)
fu,av (%), median (min-max)	ND	N/A	N/A	0.61 (0.54-0.70)[j]

AUC/dose, area under the plasma concentration-time curve from time 0 to infinity divided by dose; $AUC_{(0-t)}$/dose, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration divided by dose; C_{max}/dose, maximum plasma observed concentration divided by dose; CL/F, apparent oral plasma clearance; max, maximum; min, minimum; fu,av, average fraction unbound; $MR_{AUC(0-t)}$, metabolite-to-parent $AUC_{(0-t)}$ ratio; MR_{Cmax}, metabolite-to-parent C_{max} ratio; N/A, not applicable; ND, not determined; SD, standard deviation; t_{max}, time to C_{max}; $t_{1/2}$, terminal half-life.

[a]Child-Pugh class A (single oral dose of selumetinib 50 mg).

[b]Child-Pugh class B (single oral dose of selumetinib 50 mg [N = 6] or selumetinib 25 mg [N = 2]; dose-normalized parameters include subjects who received both the 25 and 50 mg doses, while other parameters include subjects who received the 50 mg dose only).

[c]Child-Pugh class C (single oral dose of selumetinib 20 mg).

[d]Single oral dose of selumetinib 50 mg.

[e]Data shown as geometric mean (geometric coefficient of variation [%]) unless otherwise stated.

[f]N = 6.

[g]N = 2.

[h]N = 3.

[i]N = 5.

[j]N = 4.

selumetinib to healthy subjects was 0.35% (range 0.28% to 0.45%) (Table 5). This appeared to be largely unchanged in subjects with mild or moderate hepatic impairment (≤20% difference compared with healthy subjects); however, higher unbound fractions in subjects with severe hepatic impairment were detected, which equates to a ~90% increase in the unbound fraction.

Similar to total exposure, unbound dose-normalized selumetinib exposure was lower in subjects with mild hepatic impairment and higher in subjects with moderate hepatic impairment, compared with healthy subjects (Table 5). Due to the higher unbound fraction seen in subjects with severe hepatic impairment, unbound dose-normalized selumetinib exposure was much higher with increases in AUC_u/dose and $C_{max,u}$/dose of approximately 3- and 2-fold, respectively, compared to healthy subjects.

Metabolite-to-parent ratios for $AUC_{(0-t)}$/dose ($MR_{AUC(0-t)}$/dose) and C_{max}/dose (MR_{Cmax}/dose) were greatest in healthy subjects, and decreased with worsening hepatic function. $MR_{AUC(0-t)}$/dose was 0.0930, 0.0542, and 0.0221 in healthy subjects and in subjects with mild or moderate hepatic impairment, respectively, and MR_{Cmax}/dose was 0.0957, 0.0543, and 0.0229, respectively.

N-desmethyl selumetinib dose-normalized exposure decreased with worsening hepatic function. Compared with healthy subjects, N-desmethyl selumetinib $AUC_{(0-t)}$/dose in subjects with mild hepatic impairment was 49% lower; C_{max}/dose was 56% lower. In the moderate impairment group, $AUC_{(0-t)}$/dose was 62% lower than in healthy subjects; C_{max}/dose was 70% lower. There were insufficient quantifiable concentrations of N-desmethyl selumetinib in the severe hepatic impairment group for inclusion in these comparative statistical analyses.

The regression analysis indicated that increasing Child-Pugh score, decreasing serum albumin, and increasing prothrombin time correlated with increas-

Table 5. Comparison of Key Selumetinib and N-Desmethyl Selumetinib Pharmacokinetic Parameters According to Hepatic Group (Mild,[a] Moderate,[b] Severe,[c] or Healthy[d])

	Healthy	Mild	Moderate	Severe
Selumetinib				
AUC/dose (ng·h/mL/mg)	53.64	45.93	85.11	84.29
Hepatic impairment/healthy ratio (%) (90%CI)		85.64 (64.42, 113.84)	158.68 (119.36, 210.94)	157.15 (118.21, 208.90)
AUC_u/dose (ng·h/mL/mg)	0.1837	0.1271	0.2585	0.5828
Hepatic impairment/healthy ratio (%) (90%CI)		69.18 (48.77, 98.15)	140.69 (99.17, 199.59)	317.19 (223.59, 449.98)
C_{max}/dose (ng/mL/mg)	18.88	14.82	23.57	18.53
Hepatic impairment/healthy ratio (%) (90%CI)		78.47 (55.24, 111.45)	124.84 (87.89, 177.32)	98.13 (69.08, 139.38)
$C_{max,u}$/dose (ng/mL/mg)	0.06473	0.04094	0.07165	0.1280
Hepatic impairment/healthy ratio (%) (90%CI)		63.25 (41.13, 97.26)	110.68 (71.98, 170.19)	197.66 (128.54, 303.95)
N-desmethyl selumetinib				
$AUC_{(0-t)}$/dose (ng·h/mL/mg)	4.841	2.445	1.826	ND
Hepatic impairment/healthy ratio (%) (90%CI)		50.51 (28.28, 90.19)	37.72 (21.12, 67.37)	
C_{max}/dose (ng/mL/mg)	1.809	0.8041	0.5485	ND
Hepatic impairment/healthy ratio (%) (90%CI)		44.44 (25.70, 76.85)	30.31 (17.53, 52.42)	

Data presented as geometric least-squares means. Results based on an analysis of variance model using the logarithm of parameters as the response variable and hepatic impairment group as a fixed effect (severe subjects were not included in the analyses for N-desmethyl selumetinib due to insufficient data. AUC/dose, area under the plasma concentration-time curve from time 0 to infinity divided by dose; AUC_u/dose, unbound area under the plasma concentration-time curve from time 0 to infinity divided by dose; $AUC_{(0-t)}$/dose, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration divided by dose; CI, confidence interval; C_{max}/dose, maximum observed plasma concentration divided by dose; $C_{max,u}$/dose, unbound maximum observed plasma concentration divided by dose; ND, not determined.

[a]Child-Pugh class A (single oral dose of selumetinib 50 mg) (N = 8).

[b]Child-Pugh class B (single oral dose of selumetinib 50 mg [N = 6] or selumetinib 25 mg [N = 2]).

[c]Child-Pugh class C (single oral dose of selumetinib 20 mg) (N = 8).

[d]Single oral dose of selumetinib 50 mg (N = 8).

[e]N = 6.

ing unbound selumetinib exposure (Supplemental Table S5) and decreasing N-desmethyl selumetinib exposure. A large proportion of the variability observed for unbound dose-normalized selumetinib exposure could be explained by albumin or Child-Pugh score, as indicated by the coefficient of determination values. The correlation would be less strong if normal subjects could be included.

Selumetinib and N-desmethyl selumetinib were minimally excreted in urine. In healthy subjects, 0.44% and 0.78% of the dose was excreted, respectively. The fraction of selumetinib excreted in urine was similar in subjects with mild (0.46%) and moderate (0.50%) hepatic impairment and was slightly higher in subjects with severe hepatic impairment (0.90%). N-desmethyl selumetinib excretion decreased as the severity of hepatic impairment increased (0.64%, 0.20%, and 0.09% of the dose in subjects with mild, moderate, and severe hepatic impairment, respectively).

Safety

There were no deaths, serious AEs, or discontinuations due to AEs in any of the studies. All reported AEs had resolved by the end of each study. There were no trends or safety concerns in clinical laboratory parameters, vital signs, ECG, or ophthalmological or physical assessments that were considered clinically relevant or significant in any of the studies.

Renal Impairment Study. Two subjects (8.4%) with ESRD reported AEs; both were considered unrelated to selumetinib. One subject with ESRD experienced mild diarrhea during treatment period 2 (day 2), and 1 subject reported moderate back pain and pain in an extremity (worsening bilateral arm pain) during treatment period 1 (day 1). No AEs were reported in healthy subjects.

Hepatic Impairment Study. Overall, 5 (15.6%) subjects reported at least 1 AE during the study, and these were of either mild or moderate severity. The most frequently reported AEs were diarrhea and vomiting (N = 2; 6.3% each). Two subjects (6.3%) had AEs considered related to selumetinib by the investigator: 1 subject with moderate hepatic impairment (dosed with selumetinib 50 mg) experienced moderate diarrhea, and 1 healthy subject experienced mild rash.

Discussion

The 2 studies described here provide important information regarding the PK, safety, and tolerability of single oral doses of selumetinib in otherwise healthy subjects with impaired renal or hepatic function. The results give an indication of the PK profile of selumetinib in patients with renal or hepatic impairment; this is important given that (1) drugs should be evaluated in populations in whom they are likely to be

used, and (2) a certain proportion of cancer patients who receive selumetinib may develop some degree of renal or hepatic impairment during treatment. The data described here are valuable because clinical studies generally do not assess the effect of drugs in patients with renal or hepatic impairment because these patients often do not meet the inclusion criteria. Hepatic studies can be particularly challenging to conduct; unlike creatinine clearance in patients with renal impairment, there are no well-established markers for measuring hepatic function in terms of drug elimination, and hepatic impairment can have complex effects on the PK of a given drug, including how it is absorbed, distributed, metabolized, and eliminated.

Renal Impairment Study

Data from early clinical studies show that very little selumetinib is excreted in urine in humans (NCT01931761).[6] For this reason it was anticipated that renal impairment would not produce large increases in exposure or reductions in the excretion of selumetinib. In the renal impairment study there was no evidence that renal impairment increased PK exposure to selumetinib and N-desmethyl selumetinib; indeed, total selumetinib average exposures were found to be lower in the ESRD group than in healthy subjects, which is likely a chance finding due to the small sample size, and no difference in unbound exposures was found due to the ESRD group showing higher unbound levels of selumetinib compared with healthy subjects.

According to the US FDA, even when renal impairment is likely to have little or no effect on the PK of a given drug, the impact of dialysis should be considered. This is because the dialysis process can remove a significant fraction of the drug or active metabolites in the body, necessitating dose adjustments.[10] Data from the renal impairment study showed that total selumetinib exposure was lower when selumetinib was dosed before vs after dialysis in the ESRD group. However, the difference in AUC was limited (selumetinib AUC was 17% lower before dialysis than after; Supplemental Table S1), interindividual exposure was variable, and any decreases in exposure could not be explained by dialysis, as selumetinib was not dialyzed to any meaningful extent. This was evidenced by (1) a selumetinib fraction excreted in urine of 0.922% in subjects with ESRD and (2) a dialysis clearance in subjects with ESRD that was approximately 3% of CL/F in the healthy subjects group (0.578 vs 19.1 L/h). Taken together, these data indicate that dialysis is unlikely to be beneficial to treat selumetinib overdose. Total N-desmethyl selumetinib exposure did not decrease to a meaningful extent when dosed before vs after dialysis (Table S1), and, as with the parent compound, individual exposure was highly variable. An increase in unbound levels in subjects with ESRD by ~40% compared to healthy subjects was also detected; however, no effect on unbound selumetinib exposure was found between subjects with ESRD and healthy subjects.

Hepatic Impairment Study

In vitro experiments show that selumetinib is metabolized to phase I metabolites and glucuronide conjugates. Collectively, clinical data indicate that the metabolism of selumetinib is primarily hepatic,[16] and excretion is predominantly via the feces (NCT01931761).[6] Given the role of the liver in the metabolism of selumetinib, hepatic impairment could lead to increased drug exposure.

Dose-normalized data showed that subjects with mild hepatic impairment had decreased exposure to total and unbound selumetinib compared with healthy subjects. This is most likely a chance finding due to the small sample size. In contrast, dose-normalized total and unbound selumetinib exposures were increased in subjects with moderate and severe hepatic impairment compared with healthy subjects; the 1 exception to this was total selumetinib C_{max}/dose in the severe hepatic impairment group, which was similar to those of healthy subjects. Worsening hepatic function (ie, increasing Child-Pugh score, decreasing serum albumin, and increasing prothrombin time) appeared to be correlated with increasing unbound selumetinib exposure. Selumetinib and the active metabolite N-desmethyl selumetinib are highly bound to plasma proteins with small unbound fractions (median unbound fractions of selumetinib and N-desmethyl selumetinib in the healthy subjects were similar at ~0.4% and ~0.6%, respectively, in both studies); hence, any small changes in the unbound fraction can potentially have marked effects on unbound drug concentrations. The unbound fraction of selumetinib was largely unchanged in subjects with mild or moderate hepatic impairment compared to healthy subjects; however, there was a trend toward higher unbound fraction in subjects with severe hepatic impairment that equates to a ~90% increase in the unbound fraction. This resulted in a much higher unbound dose-normalized selumetinib exposure by 3- and 2-fold for AUC_u/dose and $C_{max,u}$/dose, respectively, in subjects with severe hepatic impairment compared to healthy subjects.

The higher unbound fractions and hence lower plasma protein binding detected in subjects with ESRD and in subjects with severe hepatic impairment, compared with healthy subjects (~40% and 90%, respectively), were likely the result of altered amounts of plasma proteins available for binding. However, it should be noted that as the unbound fraction was <1%, any small percentage changes in the unbound fraction can have a large impact on variability within

the data set. There is a possibility that the change in protein binding in the severe hepatic group may alter the PK linearity that has previously been shown for selumetinib at this dose range; nonetheless, as this could not be determined in the present study, the dose normalization allows an estimation for a reasonable dose level for severe hepatic impaired subjects, which would likely give equivalent exposure to the therapeutic dose in subjects with normal hepatic function, along with the advice of continual safety monitoring of these subjects.

Regarding N-desmethyl selumetinib, dose-normalized exposure was highest in healthy subjects and was comparatively decreased in subjects with mild and moderate hepatic impairment. The severe hepatic impairment group had limited quantifiable concentrations and hence insufficient exposure parameters to conduct a comparable analysis; this could be due to a combination of worsening hepatic impairment and the lower dose of selumetinib (20 mg) administered. Decreasing N-desmethyl selumetinib exposure appeared to be correlated with worsening hepatic impairment.

Applicability of the Data. The renal and hepatic impairment studies were conducted as required by the relevant regulatory authorities, and the results of both studies will be used to determine any suitable restrictions in selumetinib use and/or to inform any necessary dose adjustments in the setting of abnormal kidney or liver function. The results from subjects with ESRD undergoing hemodialysis will also be used for consideration in dosing adjustments for patients with ESRD and the value of hemodialysis in overdose situations. At present, subjects with a CrCL <50 mL/min are excluded from clinical studies investigating selumetinib, and the findings from the renal impairment study suggest that if patients enrolled in selumetinib clinical trials develop worsening renal function, the renal failure alone is unlikely to result in increased selumetinib exposure.

Study Limitations. There are some recognized limitations to the studies described here. First, both studies collected PK data following single oral doses of selumetinib in subjects with renal or hepatic impairment but who were otherwise generally healthy. Consequently, the results of these studies are for guidance only and cannot be directly applied to oncology patients with renal or/and hepatic impairment. In such patient populations, PK modeling using data from phase II and III clinical trials will be used to inform potential changes in selumetinib exposure. The same is true for the safety and tolerability data generated in the studies; although selumetinib was well tolerated as a single oral dose and no new safety concerns were identified, outcomes in these studies cannot be directly applied to oncology patients treated with continuous twice-daily dosing of selumetinib. Second, in both studies, due to the low unbound fraction and selumetinib PK, it was not possible to measure the unbound concentrations of selumetinib and N-desmethyl selumetinib at 2 of the 3 planned time points of measurement, as they were below the lower limit of quantification of the assay. Accordingly, the lower limit of quantification was decreased and revalidated, but it was still not possible to detect concentrations at the later PK time points. Measurements were therefore taken at the 3 highest total concentrations of each subject. An absence of concentration-dependent protein binding was assumed, which was supported by the range of data that was measureable. Third, although moderate and severe hepatic impairment showed an increase in selumetinib exposure compared with healthy subjects, assessing the relationship between increased exposure and efficacy or tolerability was not an objective of these studies. Finally, subjects of Japanese or non-Japanese Asian ethnicity were excluded from our studies, and currently there are no data to evaluate potential ethnic PK differences for impaired renal and hepatic function. Preliminary data indicate that Japanese and non-Japanese Asian subjects experience higher systemic drug exposure compared with non-Asian healthy subjects who received the same dose of selumetinib (unpublished data, ethnicity pooled analysis); thus, in Japanese and non-Japanese Asian subjects with liver impairment, the magnitude of increase in exposure may not be the same as that seen in non-Asian subjects with liver impairment compared with healthy non-Asian subjects.

Conclusions

There was no increase in exposure to selumetinib or N-desmethyl selumetinib in subjects with ESRD when selumetinib was administered before or after dialysis, compared with healthy subjects, suggesting that no dose adjustment is required in patients with renal impairment and that dialysis cannot be used to treat selumetinib overdose. In contrast, exposure to selumetinib was increased in subjects with moderate and severe hepatic impairment. These findings, combined with additional research, can be used to guide required dose adjustments in these populations.

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