Clinical Study Report Synopsis

Drug Substance	Selumetinib
Study Code	D1532C00081
Edition Number	1
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An Open-label Comparative Study of the Pharmacokinetics, Safety and Tolerability of Selumetinib (AZD6244, ARRY-142886) (Hyd-Sulfate) following a Single Oral Dose in Subjects with Renal Impairment and Healthy Subjects

Study dates: First subject enrolled: 14 March 2014
Last subject last visit: 03 July 2014

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study center

This study was conducted at a single study center, Orlando Clinical Research Center, 5055 S Orange Avenue, Orlando, Florida, United States of America, under the direction of Thomas C Marbury.

Publications

There were no publications at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	PK	To investigate the PK of a single 50 mg administration of selumetinib in subjects with ESRD compared to healthy subjects.	Primary: selumetinib C_{max} and AUC [or $AUC_{(0-t)}$] Secondary: selumetinib t_{max}, $AUC_{(0-12)}$, $AUC_{(1-5),}$ λ_z, $t_{1/2}$, CL/F, V_{ss}/F, V_z/F, MRT, f_u, $f_{u,av,}$ $C_{max,u}$, AUC_u, $AUC_{(0-t),u}$, CL/F_u, A_e, f_e, CL_R, $A_{d(1-5)}$, CL_D
Secondary	Safety	To further assess the safety and tolerability of a single 50 mg oral administration of selumetinib in subjects with ESRD and in healthy subjects.	adverse events, physical examination, ophthalmitic assessments, vital signs, clinical laboratory assessments and 12-lead electrocardiogram
	PK	To characterize the PK of the N-desmethyl and amide metabolites after oral administration of single doses of selumetinib in subjects with ESRD and in healthy subjects.	N-desmethyl selumetinib (and amide metabolite, if possible) C_{max}, AUC, $AUC_{(0-t),}$ t_{max}, $AUC_{(0-12)}$, λ_z, $t_{1/2}$, f_u, $f_{u,av}$ $C_{max,u}$, AUC_u, $AUC_{(0-t),u}$, A_e, f_e, CL_R, MR_{AUC}, MR_{Cmax}, $AUC_{(1-5)}$, $A_{d(1-5)}$, CL_D

$A_{d(1-5)}$: Cumulative amount of analyte excreted in dialysis over the 4 hour dialysis period; A_e: Amount of analyte excreted in the urine; AUC: Area under plasma concentration-time curve from zero to infinity; AUC_u: Unbound area under plasma concentration-time curve from zero to infinity; $AUC_{(1-5)}$: Area under plasma concentration-time curve from 1 to 5 hours postdose; $AUC_{(0-12)}$:Area under plasma concentration-time curve from zero to 12 hours postdose; $AUC_{(0-t)}$: Area under plasma concentration-time curve from zero to last quantifiable time point; $AUC_{(0-t),u}$: Unbound area under plasma concentration-time curve from zero to last quantifiable time point; CL/F: Apparent clearance; CL/F_u: Unbound apparent oral clearance; CL_D: Dialysis clearance; CL_R: Renal clearance; C_{max}: Maximum observed plasma concentration; $C_{max,u}$: Maximum unbound observed plasma concentration; CSP: Clinical study protocol; f_e: Fraction excreted in urine; f_u: Fraction unbound; MR_{AUC}: Metabolite to selumetinib AUC ratio; MR_{Cmax}: Metabolite to selumetinib C_{max} ratio; MRT: Mean residence time; $t_{1/2}$: Terminal half life; t_{max}: Time to $C_{max;}$ V_{ss}/F: Apparent volume of distribution at steady state; V_z/F: Apparent volume of distribution; λ_z: terminal rate constant.

Study design

This study was an, open-label, comparative, 2-part (Stage 1 and Stage 2) design conducted at 1 study center.

Up to 48 subjects were to be classified at screening on the basis of their renal function, using the Cockroft-Gault formula to estimate creatinine clearance (CrCL):

$$\text{Estimated CrCL (mL/min)} = \frac{(140\text{-age [years]}) \times (\text{body weight [kg]}) \times (0.85)^{a}}{\text{Serum creatinine (mg/dL)} \times 72}$$

[a] for females

Stage 1

Stage 1 was an open-label, comparative group study in which 12 evaluable subjects with end-stage renal disease (ESRD) requiring dialysis (Group 5) and 12 healthy subjects (Group 1) participated.

Subjects with ESRD (Group 5) participated in 2 treatment periods in order to study these subjects under both non-dialysis and dialysis conditions. Subjects visited the study center for screening within 28 days of the first investigational product administration (Visit 1). Written informed consent was obtained prior to any study procedures. Subjects were admitted to the study center in the morning of Day -1.

Twelve healthy subjects in Group 1 participated in 1 treatment period, where they received a single oral administration of 50 mg selumetinib (2 x 25 mg capsules), on the morning of Day 1 (Visit 2) with approximately 240 mL of water. Healthy subjects fasted from 2 hours before investigational product administration (water was allowed up to 1 hour before administration of investigational product for the consumption of the investigational product [240 mL]) and remain fasted for 4 hours after investigational product administration. Healthy subjects (Group 1) returned to the study center for a follow-up visit (Visit 3) 3 to 7 days after the last investigational product administration.

Twelve subjects in Group 5 with ESRD requiring dialysis participated in 2 treatment periods in order to study these subjects under both non-dialysis and dialysis conditions. There was a washout period of at least 7 days between investigational product administrations. In Treatment period 1, subjects received a single oral administration of 50 mg (2 x 25 mg capsules), on Day 1 after completion of a dialysis session (Visit 2). Subjects fasted from 2 hours before investigational product administration (water was allowed up to 1 hour before administration of investigational product for the consumption of the investigational product [240 mL]) and remain fasted for 4 hours after investigational product administration. Subjects remained in the study center until the start of their next dialysis session, 72 hours postdose. Subjects returned to the study center after a washout period of at least 7 days from the first investigational product administration and admitted on Day -1 for Treatment period 2 (Visit 3).

On Day 1 of Treatment period 2, the ESRD group (Group 5) received a single oral 50 mg selumetinib (2 x 25 mg capsules), under fasted conditions (as in Treatment Period 1), 1 hour

prior to the start of a dialysis session. Subjects remained in the study center until the completion of the study assessments and procedures scheduled on Day 4 of Treatment period 2.

Subjects returned to the study center for a follow-up visit (Visit 4) 3 to 7 days following discharge.

All available safety, tolerability and PK data from Stage 1 were reviewed to assess the effect of renal impairment on selumetinib. A decision was made by the SRC to determine whether to conduct Stage 2 and which renal impairment group(s) to include.

Stage 2

Stage 2 of the study was to be conducted only if renal impairment in the 12 subjects with ESRD (Group 5) in Stage 1 showed a difference in selumetinib exposure as defined by the ESRD group mean area under the plasma concentration-time curve from zero to infinity (AUC) of selumetinib being >1.5 x the group mean of healthy subjects (8 subjects or 12 subjects). In this study, Stage 2 was not conducted.

Target subject population and sample size

Subjects were classified at screening on the basis of their renal function using the CrCL. Healthy subjects with normal renal function (CrCL 80 mL/min) were matched for gender, age (±10 years) and body mass index (BMI) (±15%) to the mean age and BMI of subjects in the ESRD group.

All 24 enrolled subjects completed the treatments and 23 subjects completed the study; Subject E00010029 (normal cohort) withdrew consent to participate in the study after receiving selumetinib, on Day 3.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Table S2 Details of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer	Batch number
Selumetinib hyd-sulphate	25 mg blue oral capsules (containing 25 mg free base equivalent of selumetinib hyd-sulfate)	Patheon, Cincinnati, United States	46940.1/41957.1

All investigational products were kept in a secure place under appropriate storage conditions.

Duration of treatment

The study duration in the study for healthy subjects included 3 visits, approximately 5 weeks: a maximum of 28 days (relative to Day 1) for screening (Visit 1), a 4-day residency (Visit 2), and a follow-up visit 3 to 7 days following discharge (Visit 3).

The study duration for subjects in the ESRD group (Group 5) include 4 visits and be approximately 6 weeks: a maximum of 28 days (relative to Day 1) for screening (Visit 1), 2 periods of a 4-day residency (Visits 2 and 3), and a follow-up visit 3 to 7 days following discharge at Treatment period 2 (Visit 4).

Statistical methods

Pharmacokinetic data were listed and summarized by renal function group, as appropriate.

For statistical evaluation of renal impairment, log-transformed pharmacokinetic parameters of selumetinib (maximum observed plasma concentration [C_{max}], AUC, maximum unbound plasma concentration [$C_{max,u}$], and unbound area under plasma concentration-time curve from zero to infinity [AUC_u]) and N-desmethyl selumetinib (C_{max} and AUC) were separately analyzed using a linear fixed effect analysis of variance model. Geometric least-squares means together with confidence intervals (2-sided 95%) were estimated and presented. Also, ratios of geometric least-squares means (ESRD versus normal) together with confidence intervals (2-sided 90%) were estimated and presented. For ESRD subjects, only data from off dialysis (Treatment Period 1) were included in these analyses.

To assess the potential differences between Treatment Period 1 (off dialysis) and Treatment Period 2 (on dialysis) in ESRD subjects, C_{max} and AUC were analyzed using a repeated measures analysis of variance model on the log-transformed data. Geometric least-squares means together with confidence intervals (2-sided 95%) were estimated and presented. Also, ratios of geometric least-squares means together with confidence intervals (2-sided 90%) were estimated and presented.

The AEs were coded using the Medical Dictionary for Regulatory Activities for System Organ Class (SOC) and Preferred Term (PT). Adverse events were summarized for each renal group by SOC and PT. Medications were classified according to the AstraZeneca Drug Dictionary.

Tabulations and listings of data for frequency and severity of AEs and results of clinical laboratory tests, vital signs, electrocardiograms, and physical examinations were presented by renal group. The safety data was presented by renal group and included all subjects who received at least one dose of investigational product. For clinical laboratory tests, listings of values for each subject were presented with abnormal or out of range values flagged.

Subject population

The minimum age of the subjects in the study was 36 years, which was in accordance with the protocol defined age limit (18 years or more) with a mean age of 50 years. The majority of subjects were males (20/24; 83.3%). Most of the subjects were of Not-Hispanic or Latino (19/24; 79.2%) in ethnicity. There were more subjects of Black or African American (16/24; 66.7%) origin as compared to subjects of White (8/24; 33.3%) origin in this study. The BMI of the subjects ranged from 19.1 kg/m^2 to 36.3 kg/m^2 with a minimum weight of 50.6 kg, which was in accordance with the inclusion criteria.

Subject E00010036 had a CrCL value classified as normal at screening (82.05 mL/min), but on Day -1 the CrCL was calculated as 70.99 mL/min due to the subject's dehydrated state which would re-classify this subject in the mild renal impairment cohort. The subject could not be moved into a different renal group, as this study only included those with normal renal function and ESRD. As this could possibly impact PK, Subject E00010036 was excluded from the PK analysis set and all summaries, and included in listings only.

Summary of pharmacokinetic results

Table S3 summarizes the ratios of the geometric means for both selumetinib and N-desmethyl selumetinib key PK parameters between the ESRD group in Period 1 and the normal group.

Table S3 Statistical comparison of key pharmacokinetic exposure parameters by renal group

				Comparison of ESRD/Normal		
Analyte	**Parameter (units)**	**Renal group**	**n**	**Geometric LS Mean**	**Ratio (%)**	**90% CI**
Selumetinib	AUC (ng·h/mL)	ESRD	12	1881		
		Normal	11	2617	71.89	(58.20, 88.79)
	AUC_u (ng·h/mL)	ESRD	12	10.25		
		Normal	11	10.55	97.13	(83.36, 113.17)
	C_{max} (ng/mL)	ESRD	12	724.6		
		Normal	11	863.4	83.92	(62.12, 113.37)
	$C_{max,u}$ (ng/mL	ESRD	12	3.945		
		Normal	11	3.484	113.23	(86.66, 147.95)
N-desmethyl selumetinib	AUC (ng·h/mL)	ESRD	11	171.0		
		Normal	11	185.9	91.95	(67.73, 124.83)
	C_{max} (ng/mL)	ESRD	12	45.15		
		Normal	11	53.45	84.48	(61.60, 115.86)

AUC: Area under the plasma concentration-time curve from time zero to infinity; AUC_u: Unbound area under the plasma concentration-time curve from time zero to infinity CI: Confidence interval; C_{max}: Maximum observed concentration in plasma; $C_{max,u}$: Unbound maximum observed concentration in plasma; LS: Least squares
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.
Normal: CrCL greater than 80 mL/min; single 50 mg administration of selumetinib on Day 1;
ESRD: Requiring hemodialysis:
Treatment Period 1: single 50 mg administration of selumetinib on Day 1 after completion of a dialysis session.
Treatment Period 2: single 50 mg dose of selumetinib, 1 hour prior to the start of a dialysis session.

Total selumetinib maximum observed concentration (C_{max}) and total overall selumetinib exposure (AUC) were 16% and 28% lower, respectively, in the ESRD group compared to the normal group. However, unbound selumetinib overall exposure (AUC_u) appeared to be the same between groups (geometric least-squares mean ratio of 97.13%), with the 90% CI of (83.36%, 113.17%) completely contained within 80% to 125%, while unbound selumetinib maximum observed concentration ($C_{max,u}$) was 13% higher in the ESRD group when compared to the normal group.

Similar to selumetinib, total N-desmethyl selumetinib exposure was lower in the ESRD group compared to the normal group. Maximum observed concentration (C_{max}) and total overall N-desmethyl selumetinib exposure (AUC) were 16% and 8% lower, respectively, in the ESRD group compared to the normal group.

Table S4 summarizes the ratios of the geometric means for both selumetinib and N-desmethyl selumetinib AUC and C_{max} in the ESRD group when selumetinib was given before dialysis (Treatment Period 2) compared to when selumetinib was given after dialysis (Treatment Period 1).

Table S4 Statistical comparison of key pharmacokinetic exposure parameters in the ESRD group by dialysis status

				Comparison of Period 2/Period 1		
Analyte	**Parameter (units)**	**Treatment Period**	**n**	**Geometric LS Mean**	**Ratio (%)**	**90% CI**
Selumetinib	AUC (ng·h/mL)	Period 1	12	1881		
		Period 2	12	1556	82.68	(73.58, 92.91)
	C_{max} (ng/mL)	Period 1	12	724.6		
		Period 2	12	507.1	69.99	(52.88, 92.64)
N-desmethyl selumetinib	AUC (ng·h/mL)	Period 1	11	171.0		
		Period 2	11	153.2	89.60	(75.25, 106.69)
	C_{max} (ng/mL)	Period 1	12	45.15		
		Period 2	12	38.49	85.25	(68.80, 105.64)

AUC: Area under the plasma concentration-time curve from time zero to infinity; CI: Confidence interval; C_{max}: Maximum observed concentration in plasma LS: Least squares
Results based on repeated measured analysis of variance model using the logarithm of AUC and Cmax as the response variable and period as a repeated-fixed effect.
ESRD: Requiring hemodialysis:
Treatment Period 1: single 50 mg administration of selumetinib on Day 1 after completion of a dialysis session.
Treatment Period 2: single 50 mg dose of selumetinib, 1 hour prior to the start of a dialysis session.

Total selumetinib maximum (C_{max}) and total overall selumetinib exposure (AUC) were 30% and 17% lower, respectively, when selumetinib was dosed before dialysis (Treatment Period 2) than after (Treatment Period 1). Similar to selumetinib, total N-desmethyl selumetinib maximum (C_{max}) and total overall N-desmethyl selumetinib exposure (AUC) were 15% and 10% lower, respectively, when selumetinib was dosed before dialysis (Treatment Period 2) than after (Treatment Period 1).

Summary of safety results

- No deaths, serious AEs (SAEs), discontinuation of investigational product due to an AE (DAEs), or other significant AEs (OAEs) were reported in the study

- Overall 2 subjects with ESRD reported at least 1 AE during the study. One subject with ESRD reported at least 1 AE during Treatment period 1 (Subject E00010010 reported a mild AE of diarrhoea) and Treatment period 2 (Subject E00010013 reported moderate AEs of back pain and pain in extremity) respectively. There were no AEs reported for any healthy subjects. None of the AEs were considered causally related to the investigational product by the principal investigator

- Variation, with no trend over time and between treatments, was observed in the laboratory variables, vital signs measurements, and electrocardiogram (ECG) measurements. Although abnormal 12-lead ECG readings were reported during the study, none were considered clinically significant by the principal investigator

- No clinically significant abnormal physical examination findings were reported in the study or reported as AEs