Clinical Study Report Synopsis

Drug Substance	Selumetinib
Study Code	D1532C00085
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A Phase I Open-label, Single-center Study to Assess the Effect of the CYP3A4 inducer Rifampicin on the Pharmacokinetics of a 75 mg Single Oral Dose of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Healthy Volunteers aged 18 to 45 years

Study dates: First subject enrolled: 04 February 2014
Last subject last visit: 04 April 2014

Phase of development: Clinical pharmacology Phase 1

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, Quintiles Phase 1 unit, Overland Park, Kansas, United States, under the direction of Dr Eleanor Lisbon.

Publications

None 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 effect of multiple 600 mg oral doses of rifampicin on the exposure of a single 75 mg oral dose of selumetinib in healthy volunteers	The primary PK parameters were selumetinib AUC, $C_{max,}$ and $AUC_{(0-t)}$. The secondary PK parameters were selumetinib t_{max}, $AUC_{(0-12)}$, λ_z, $t_{½}$, CL/F, V_{ss}/F, V_z/F, and MRT
Secondary	PK	To investigate the PK of N-desmethyl selumetinib when selumetinib is administered with or without rifampicin.	N-desmethyl selumetinib AUC, C_{max}, t_{max}, $\lambda_{z,}$ $t_{½}$, $AUC_{(0-12)}$, $AUC_{(0-t)}$, MR_{AUC}, and MRC_{max}.
		To determine the plasma concentration of rifampicin at 2 hours after administration during the rifampicin dosing period to monitor the exposure of the cytochrome P450 (CYP)3A4 inducer.	The 2 hours postdose plasma concentrations.
		To determine the 4β-hydroxycholesterol to cholesterol concentration ratios as a marker of CYP3A4 induction by rifampicin.	Ratio of post-treatment (Day 12 or Day 14) to pre-treatment (Day 4 predose) concentration.
	Safety	To further assess the safety and tolerability of selumetinib by the assessment of AEs, laboratory variables, and vital signs.	AEs, physical examinations, ophthalmologic assessments, vital signs, clinical laboratory assessments, and 12-lead ECG.

AE: Adverse event; AUC: Area under the plasma concentration-time curve from time zero to infinity; $AUC_{(0-t)}$: Area under plasma concentration-time curve to time of last measurable concentration; $AUC_{(0-12)}$: Area under the plasma concentration time curve from zero to 12 hours postdose; C_{max}: Maximum observed plasma concentration; CL/F: Apparent oral clearance; CYP3A4: Cytochrome P450 3A4; ECG: Electrocardiogram; PK: Pharmacokinetic; MR_{AUC}: Metabolite to parent AUC; MR_{Cmax}: Metabolite to parent C_{max}; MRT: Mean residence

time; $t_{1/2}$: Terminal elimination half-life; t_{max}: Time to reach maximum observed concentration administration; V_{ss}/F: Apparent volume of distribution at steady state; Vz/F: Apparent volume of distribution during the terminal phase; λ_z: Terminal rate constant

Study design

This Phase I clinical study was designed as an open-label, fixed sequence, single-center study to investigate the effect of rifampicin on the pharmacokinetics (PK), safety and tolerability of a single 75 mg oral dose of selumetinib in healthy male and female (of non-childbearing potential) volunteers. Approximately 24 healthy volunteers aged between 18 to 45 years (inclusive), were to be enrolled in the study. Screening procedures were performed for healthy volunteers who provide written informed consent.

The study consisted of 3 visits. Visit 1 was a screening visit and took place within 28 days of Visit 2. Visit 2 was the treatment visit and the healthy volunteers were resident at the study center from Day -1 up to Day 15. Visit 3 was the follow-up visit and took place 7 to 10 days after discharge on Day 15, Visit 2.

Healthy volunteers were assigned to the following treatment schedules:

- Treatment A: Healthy volunteers received a single oral dose of 75 mg (3 x 25 mg) selumetinib on Day 1. Safety assessments were performed and the blood samples were collected for PK analysis until Day 4
- Treatment B: Following completion of assessments for Treatment A on Day 4, healthy volunteers received single-daily, oral doses of 600 mg rifampicin on Days 4 to 11
- Treatment C: On Day 12, healthy volunteers received 600 mg rifampicin with a single oral dose of 75 mg (3 x 25 mg) selumetinib, administered at the same time. Once-daily rifampicin administration continued through to Day 14

Safety assessments were performed and blood samples were collected for PK analyzes until Day 15.

Target subject population and sample size

Healthy male and female (of non-childbearing potential) volunteers aged 18 to 45 years (inclusive) who were non-smokers, had a body mass index (BMI) between 18 and 30 kg/m^2 (inclusive) and weighed at least 50 kg and no more than 100 kg (inclusive), had a calculated creatinine clearance greater than 50 mL/min using the Cockcroft-Gault formula.

Approximately 24 healthy volunteers were expected to be enrolled in this study. Withdrawn healthy volunteers were not replaced; however, additional volunteers were to be included in the study until such a time as 20 evaluable volunteers had completed both treatments.

A total of 22 healthy volunteers participated in this study.

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

Table S2 Identity of the investigational product

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

Additional study drug

Table S3 Additional study drug

Investigational product	Dosage form and strength	Manufacturer	Batch number
Rifampicin	300 mg oral capsules	sourced locally by the study center	2013272245

Duration of treatment

Volunteers participated in the study for approximately 8 weeks; including screening over 28 days. Volunteers were resident in the study center from Day -1 until all study assessments were completed on Day 15, with a follow-up visit 7 to 10 days after discharge (Day 15).

Statistical methods

Pharmacokinetic parameters were listed and summarized by analyte and treatment, as appropriate. Individual and geometric mean parameters were presented graphically by treatment and analyte.

Following log-transformation, C_{max}, AUC, and $AUC_{(0-t)}$ of selumetinib were separately analyzed by mixed effect analysis of variance model, fitting a fixed effect term for treatment (selumetinib + rifampicin [Treatment C] vs selumetinib alone [Treatment A]) and a random effect for volunteer. Point estimates and 90% confidence intervals (CIs) for the differences between treatment (selumetinib + rifampicin [Treatment C] and selumetinib alone [Treatment A]) were constructed. The point estimate and adjusted 90% CIs were exponentially back transformed to provide point and CI estimates for the ratio of interest [ie, C_{max}, AUC, or $AUC_{(0-t)}$ of selumetinib contrasting with or without co-administration with rifampicin].

Analyses were conducted separately for selumetinib and the metabolite N-desmethyl selumetinib.

Rifampicin concentrations were summarised by study day using appropriate descriptive statistics. Results for 4β-hydroxycholesterol and cholesterol post-treatment to pre-treatment

concentration ratios were listed and summarized by analyte and study day using descriptive statistics.

Log-transformed concentrations of 4ß-hydroxycholesterol, cholesterol, and the ratio of 4ß-hydroxycholesterol/cholesterol were separately analyzed by mixed effect analysis of variance model, fitting a fixed effect term for day and a random effect for volunteer. Point estimates and 90% CIs for the differences in days (Days 12 or 14 versus Day 4) were constructed. The point estimate and adjusted 90% CIs were exponentially back transformed to provide point and CI estimates for the ratios of interest.

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 treatment group by SOC and PT. Medications were classified according to the AstraZeneca Drug Dictionary.

Tabulations and listing of data for frequency and severity of AEs and results of clinical laboratory tests, vital signs, 12-lead electrocardiograms, and physical examinations were presented by treatment. The safety data were presented by treatment and included all healthy volunteers who received at least one dose of investigational product. For clinical laboratory tests, listings of values for each healthy volunteer were presented with abnormal or out of range values flagged.

Subject population

The majority of healthy volunteers were male (95.5%). The age of healthy volunteers ranged from 22 to 44 years (mean age of 31 years) with a BMI ranging from 21.18 to 29.69 kg/m^2 (mean BMI of 26.24 kg/m^2), in accordance with the inclusion criteria. Most of the healthy volunteers (77.3%), were Not Hispanic or Latino in ethnicity.

Summary of pharmacokinetic results

Table S4 summarizes the ratios of the geometric means for both selumetinib and N-desmethyl selumetinib AUC, $AUC_{(0-t)}$, and C_{max} when selumetinib was given alone and with rifampicin.

Table S4 Statistical comparison of key PK exposure parameters

Analyte	Parameter (units)	Treatment	N	Geometric LS Mean	Ratio (%)	90% CI
Selumetinib	AUC (ng· h/mL)	Selumetinib Alone	22	4482		
		Selumetinib + Rifampicin	22	2202	49.13	(45.91, 52.58)
	$AUC_{(0-t)}$ (ng· h/mL)	Selumetinib Alone	22	4422		
		Selumetinib + Rifampicin	22	2172	49.12	(45.90, 52.56)
	C_{max} (ng/mL)	Selumetinib Alone	22	1441		
		Selumetinib + Rifampicin	22	1068	74.07	(65.91, 83.26)

Table S4 Statistical comparison of key PK exposure parameters

Analyte	Parameter (units)	Treatment	N	Geometric LS Mean	Ratio (%)	90% CI
N-desmethyl selumetinib	AUC (ng·h/mL)	Selumetinib Alone	19	403.1		
		Selumetinib + Rifampicin	22	170.3	42.24	(39.39, 45.30)
	$AUC_{(0-t)}$ (ng·h/mL)	Selumetinib Alone	22	347.3		
		Selumetinib + Rifampicin	22	157.4	45.32	(41.87, 49.06)
	C_{max} (ng/mL)	Selumetinib Alone	22	106.4		
		Selumetinib + Rifampicin	22	86.86	81.62	(71.18, 93.59)

CI: Confidence interval; LS: Least squares
Results from a linear mixed-effects analysis of variance model using the natural logarithm of AUC, $AUC_{(0-t)}$, and C_{max} as the response variables, fixed effect for treatment, and a random effect for subject.

Source: Table 11.2.6

Rifampicin co-administration decreased selumetinib and N-desmethyl selumetinib AUC (by 50.9% and 57.8%, respectively) and C_{max} (by 25.9% and 18.4%, respectively).

Selumetinib and N-desmethyl selumetinib t_{max} were similar between treatments (1.00 h to 1.50 h), however rifampicin appeared to cause a decrease in mean $t_{1/2}$ from 9.3 h to 6.7 h for selumetinib and 9.5 h to 2.7 h for N-desmethyl selumetinib.

The statistical assessment of CYP3A4 induction as measured by 4β-hydroxycholesterol/cholesterol is summarized below in Table S5.

Cholesterol did not appear to change on Day 12 and Day 14 when compared to Day 4. However, 4β-hydroxycholesterol increased 3.5-fold on Day 12 and 4.2-fold on Day 14 when compared to Day 4. Similarly, 4β-hydroxycholesterol/cholesterol increased 3.4-fold on Day 12 and 3.8-fold on Day 14 when compared to Day 4.

Table S5 Statistical assessment of CYP3A4 induction

Analyte	Study day	N	Geometric LS mean	Ratio[a] (%)	90% CI
4β-hydroxycholesterol (ng/mL)	4	22	28.53		
	12	22	100.6	352.62	(325.50, 381.99)
	14	22	118.8	416.32	(384.31, 451.00)
Cholesterol (mg/dL)	4	22	182.9		
	12	22	186.7	102.12	(98.46, 105.92)

Table S5 Statistical assessment of CYP3A4 induction

Analyte	Study day	N	Geometric LS mean	Ratio[a] (%)	90% CI
4β-hydroxycholesterol/ cholesterol (mol/mol*104)	14	22	196.9	107.66	(103.80, 111.67)
	4	22	0.1515		
	12	22	0.5186	342.30	(317.15, 369.44)
	14	22	0.5797	382.65	(354.53, 412.99)

[a] Ratio is calculated as Day 12 or Day 14 compared to Day 4
CI: Confidence interval; LS: Least squares
Results from a linear mixed-effects analysis of variance model using the natural logarithm of 4β-hydroxycholesterol, cholesterol, and 4β-hydroxycholesterol/cholesterol as the response variables, fixed effect for days, and a random effect for subject.

Source: Table 11.2.8

Summary of safety results

- No deaths, serious adverse events (SAEs), or discontinuation of investigational product due to an AE (DAEs) were reported in this study
- Selumetinib was generally well tolerated when administered as a single oral dose of 75 mg, as well as when administered concurrently with 600 mg rifampicin
- All AEs were considered to be mild in intensity and were considered to be not related to selumetinib
- No trends were observed in hematology, biochemistry, and urinalysis parameters in this study
- There were no clinically significant 12-lead ECG findings or ophthalmological findings were reported
- There were no clinically significant abnormal laboratory, vital signs, or physical examination results reported