Clinical Study Report Synopsis

Drug Substance	Selumetinib
Study Code	D1532C00083
Edition Number	1
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A Phase I, Open-label, Single-center Study to Assess the Effect of the CYP3A4 Inhibitor Itraconazole and the CYP2C19 Inhibitor Fluconazole on the Pharmacokinetics of a 25 mg Single Oral Dose of Selumetinib (AZD6244; ARRY-142866) (Hyd-Sulfate) in Healthy Volunteers aged 18 to 45 years

Study dates: First subject enrolled: 5 March 2014
Last subject last visit: 29 April 2014

Phase of development: Clinical pharmacology (I)

Principal Investigator

Sponsor's Responsible Medical Officer:

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

Study centre(s)

This study was conducted at a single study center in the USA, Quintiles, Overland Park, Kansas.

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 effects of steady state levels of itraconazole or fluconazole on the exposure of selumetinib after a single 25 mg administration 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 was administered with or without multiple 200 mg twice daily doses of itraconazole.	N-desmethyl selumetinib AUC, C_{max}, $t_{max,}$ $\lambda_{z,}$ $t_{½}$, $AUC_{(0-12)}$, $AUC_{(0-t)}$, MR_{AUC}, and MRC_{max}.
Secondary	PK	To investigate the PK of N-desmethyl selumetinib when selumetinib was administered with or without multiple 200 mg daily doses of fluconazole (400 mg first day dose).	N-desmethyl selumetinib AUC, C_{max}, $t_{max,}$ $\lambda_{z,}$ $t_{½}$, $AUC_{(0-12)}$, $AUC_{(0-t)}$, MR_{AUC}, and MRC_{max}.
Secondary	Safety	To further assess the safety and tolerability of selumetinib by assessment of AEs, laboratory variables and vital signs.	Adverse events, clinical laboratory safety assessments, physical examinations, ECGs, ophthalmologic assessments and vital signs.
Exploratory[a]	PK	To determine variations in BCRP, CYP2C19 and UGT1A1 genotypes and their impact on selumetinib PK.	Reported separately from the CSR.
Exploratory[a]	Pharmacogenetic	To collect an optional pharmacogenetic sample from consenting healthy volunteers for exploratory investigation, to determine whether variability in PK or safety parameters can be explained by differences in the healthy volunteer's genotype.	Reported separately from the CSR.

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 quantifiable concentration; $AUC_{(0-12)}$: Area under the plasma concentration-time curve from zero to 12 hours post-dose; BRCP: Breast cancer resistance

protein; C_{max}: maximum observed plasma concentration; CL/F: Apparent oral clearance; CYP: Cytochrome p450; 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; UGT1A1: UDP glucuronosyltransferase 1A1; 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

a Reported separately from the CSR.

Study design

This was a Phase I, open-label, single-center, 2-sequence, partially randomized 3-period study in healthy volunteers in order to investigate the effect of itraconazole and fluconazole on the PK, safety and tolerability of a single administration of 25 mg selumetinib.

The study consisted of 4 visits. Visit 1 was a screening visit up to 28 days prior to Visit 2. Visit 2 comprised of 2 treatment periods, Period 1 and Period 2. Healthy volunteers were admitted on Day -1, Period 1 (Visit 2) and discharged on Day 12, Period 2 (Visit 2). Visit 3 constituted Period 3 of the treatment periods, for which healthy volunteers were admitted to the study center on Day -1 and discharged on Day 12. Visit 4 was a follow-up visit, 7 to 10 days after discharge on Day 12 (Visit 3).

Volunteers received standardized meals during residency at the study center.

Healthy volunteers were randomized to one of 2 treatment sequences on Day 1, Period 1 of Visit 2:

Sequence 1

- Period 1 (Treatment A): a single dose of 25 mg selumetinib administered alone (4 hours [h] fasted state) on Day 1, Period 1 of Visit 2 followed by a washout period of at least 4 days. The PK was assessed for 96 h post-dose (Day 1 of Period 1 to Day 1 of Period 2).

- Period 2 (Treatment B + Treatment C): 200 mg itraconazole twice daily on Day 1 to Day 11, Period 2 of Visit 2. A second administration of 25 mg selumetinib (4 h fasted state) on Day 8, followed by a washout period of at least 21 days after the last itraconazole administration.

- Period 3 (Treatment D + Treatment E): 400 mg fluconazole on Day 1, Period 3 of Visit 3 and 10 daily doses of 200 mg fluconazole from Day 2 to Day 11. A third administration of 25 mg selumetinib (4 h fasted state) on Day 8 of Visit 3.

Sequence 2

- Period 1 (Treatment A): a single dose of 25 mg selumetinib administered alone (4 h fasted state) on Day 1, Period 1 of Visit 2 followed by a washout period of at least 4 days. The PK was assessed for 96 h post-dose (Day 1 of Period 1 to Day 1 of Period 2).

- Period 2 (Treatment D + Treatment E): 400 mg fluconazole on Day 1, Period 2 of Visit 2 and 10 daily doses of 200 mg fluconazole from Day 2 to Day 11. A second administration of 25 mg selumetinib (4 h fasted state) on Day 8, followed by a washout period of at least 21 days after the last fluconazole administration.

- Period 3 (Treatment B + Treatment C): 200 mg itraconazole twice daily on Day 1, Period 3 to Day 11 of Visit 3. A second administration of 25 mg selumetinib (4 h fasted state) on Day 8, followed by a washout period of at least 21 days after the last itraconazole administration.

Target subject population and sample size

Approximately 26 healthy volunteers aged between 18 to 45 years (inclusive) were enrolled. Withdrawn healthy volunteers were not replaced; however, additional volunteers could have been included in the study to ensure at least 20 evaluable healthy volunteers complete the study for each treatment comparison (ie, itraconazole + selumetinib versus selumetinib alone and fluconazole + selumetinib versus selumetinib alone, respectively).

Planned: Approximately 26 subjects
Randomized: 26 subjects
Treated: 26 subjects
Completed treatment: 21 subjects
Completed study: 20 subjects

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 of America	3105519R

Selumetinib capsules had to be packaged in high-density polyethylene (HDPE) bottles.

Table S3 Identity of the additional study drug

Additional study drug	Dosage form and strength	Manufacturer	Batch number
Itraconazole	100 mg oral capsules	Sandoz	DR8653
Fluconazole	200 mg oral tablets	Glenmark Pharmaceuticals	02132721

Duration of treatment

The study consisted of the following periods for each subject:

Screening: 26 days
Period 1: 1 day
Washout period: 4 days
Period 2: 12 days
Washout period: 4 days
Period 3: 12 days
Follow up: 7 to 12 days following discharge on Day 12 of Period 3.

Statistical methods

Statistical analyses were performed per Quintiles Standard Operating Procedures and Work Instructions. SAS® Version 9.2 or higher and, where appropriate, additional validated software were used for all analyses and preparation of tables and listings.

Adverse events were listed for all healthy volunteers with AEs that occurred before dosing indicated on the listing. The number of AEs experienced following administration of the investigational product was summarized in tables using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0 system organ class (SOC) and preferred term (PT). These summary tables were also produced with severity and causality of AEs added as additional classification factors. The number of AEs overall, SAEs, other significant AEs, AEs that lead to withdrawal, AEs of severe intensity, and causally-related AEs were summarized. Any AE occurring post-dose were considered associated with the last dose of investigational product taken. Any AE occurring on Day -1, Period 1 (Visit 2) was not included in the summaries.

Tabulations and listings of data for vital signs, ECGs, and clinical laboratory tests were presented, as appropriate. Date and time of physical examinations were presented separately in listings only.

Pharmacokinetic variables were summarized using appropriate descriptive statistics (eg, n, arithmetic mean, coefficient of variation [CV%], standard deviation, geometric mean, geometric coefficient of variation [GCV%], minimum, median, and maximum).

Analyses were conducted for selumetinib and separately for the metabolite N-desmethyl selumetinib. However, note that sample size was determined according to the precision of the drug interaction effect on selumetinib, rather than the metabolite. Although descriptive CIs were presented for some outcomes, this study was not powered to perform any formal hypothesis testing.

Trough itraconazole and fluconazole concentrations were listed and summarized using appropriate descriptive statistics. Concentrations were graphically displayed by analyte and steady-state attainment was assessed graphically.

Subject population

In total, 26 subjects were randomized to the study and all subjects (100.0%) received treatment. Overall, 21 (80.8%) of the subjects completed treatment, while 20 (76.9%) subjects completed the study.

The demographic and baseline characteristics of the subjects were considered representative of the target population for this study.

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 itraconazole or fluconazole.

Table S4 Statistical comparison of key pharmacokinetic exposure parameters

Analyte	Parameter (units)	Treatment	N	Geometric LS Mean	Ratio (%)	90% CI
Selumetinib	AUC (ng·h/mL)	Treatment A	26	1184		
		Treatment BC	24	1767	149.30	(140.40, 158.75)
		Treatment DE	22	1815	153.30	(143.88, 163.34)
	$AUC_{(0-t)}$ (ng·h/mL)	Treatment A	26	1144		
		Treatment BC	24	1694	148.04	(139.04, 157.62)
		Treatment DE	22	1767	154.46	(144.77, 164.79)
	C_{max} (ng/mL)	Treatment A	26	408.6		
		Treatment BC	24	484.5	118.57	(104.20, 134.93)
		Treatment DE	22	512.9	125.53	(109.90, 143.38)
N-desmethyl selumetinib	AUC (ng·h/mL)	Treatment A	21	96.97		
		Treatment BC	13	89.19	91.98	(84.42, 100.21)
		Treatment DE	14	143.7	148.18	(136.08, 161.35)
	$AUC_{(0-t)}$ (ng·h/mL)	Treatment A	26	83.39		
		Treatment BC	24	74.01	88.75	(82.03, 96.03)
		Treatment DE	22	116.8	140.08	(129.14, 151.95)
	C_{max} (ng/mL)	Treatment A	26	35.67		
		Treatment BC	24	26.78	75.09	(66.71, 84.52)
		Treatment DE	22	37.75	105.83	(93.69, 119.56)

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.
Treatment A: 25 mg selumetinib alone on Day 1;
Treatment C: 200 mg itraconazole twice daily on Day 8 through Day 11 plus 25 mg selumetinib on Day 8;
Treatment E: 200 mg fluconazole once daily on Day 8 through Day 11 plus 25 mg selumetinib on Day 8.

Co-administration of both itraconazole (a CYP3A4 inhibitor) and fluconazole (a CYP2C19 inhibitor) resulted in a similar increase in exposure in selumetinib; C_{max} was approximately 19% to 26% higher, respectively, while AUC increased 49% and 53%, respectively.

When selumetinib was co-administered with itraconazole, N-desmethyl selumetinib C_{max} was 28% lower than when selumetinib was given alone, while the geometric LS ratio for $AUC_{(0-t)}$ was 88.75%. When selumetinib was co-administered with fluconazole, N-desmethyl selumetinib $AUC_{(0-t)}$ was 40% higher than when selumetinib was given alone, while the C_{max} geometric LS ratio was 105.83%.

Table S5 summarizes the statistical comparison of t_{max}. Median selumetinib t_{max} was similar when selumetinib was administered with either itraconazole or fluconazole compared to when selumetinib was given alone, with a median difference (90% CI) of 0.00 (-0.25, 0.25) and 0.01 (-0.24, 0.25), respectively.

Median N-desmethyl selumetinib t_{max} was later when selumetinib was administered with either itraconazole or fluconazole (1.50 h) compared to when selumetinib was given alone (1.00 h), with a median difference (90% CI) of 0.25 (0.00, 0.50) and 0.01 (0.00, 0.26), respectively.

Table S5 Statistical comparison of t_{max}

Analyte	Treatment	N	Median	Median Difference	90% CI for Median Difference	P-value
Selumetinib	Treatment A	26	1.00			
	Treatment C	24	1.01	0.00	(-0.25, 0.25)	0.6461
	Treatment E	22	1.50	0.01	(-0.24, 0.25)	0.6547
N-desmethyl selumetinib	Treatment A	26	1.00			
	Treatment C	24	1.50	0.25	(0.00, 0.50)	0.0366
	Treatment E	22	1.50	0.25	(0.00, 0.26)	0.0340

CI: Confidence interval; LS: Least squares; t_{max}: Time to maximum concentration in plasma
Median difference and CI calculated using the Hodges-Lehmann estimator. P-value for treatment difference in median t_{max} calculated using the Wilcoxon signed rank test.
Treatment A: 25 mg selumetinib alone on Day 1;
Treatment C: 200 mg itraconazole twice daily on Day 8 through Day 11 plus 25 mg selumetinib on Day 8;
Treatment E: 200 mg fluconazole once daily on Day 8 through Day 11 plus 25 mg selumetinib on Day 8.

Arithmetic mean selumetinib $t_{1/2}$ was slightly longer when selumetinib was given with fluconazole (9.75 h) and markedly longer when selumetinib was administered with

itraconazole (14.0 h) when compared to given alone (8.24 h). Arithmetic mean N-desmethyl selumetinib $t_{1/2}$ was similar among treatments, but not determined for many of the subjects.

Summary of safety results

The majority of randomized subjects were male (92.3%), with the overall age ranging from 18 to 44 years. The BMI ranged from 21.57 to 29.51 kg/m^2 with a minimum weight of 61.5 kg.

No deaths, SAEs or discontinuations from the study investigational product due to AEs were reported during the study. A total of 13 (50.0%) subjects reported at least one AE during the study. Overall, the highest incidence of subjects with at least one AE was reported in the SOC of Nervous System Disorders (4 [15.4%] subjects). Per treatment group, the highest incidence of subjects with at least one AE was reported in Treatment C (selumetinib and itraconazole co-administration) in the SOC of Nervous System Disorders (4 [16.7%] subjects), followed by Treatment E (selumetinib and fluconazole co-administration) in the SOC of General Disorders and Administration Site Disorders (2 [9.1%] subjects), and Treatment B (itraconazole pre-dosing) in the SOC of Gastrointestinal Disorders (2 [8.3%] subjects). Overall, the AE with the highest incidence by PT was headache, reported by 4 (15.4%) subjects. Per treatment group, the AE with the highest incidence by PT was headache, reported by 4 (16.7%) subjects in Treatment C (selumetinib and itraconazole co-administration).

No trends within or between treatment groups were identified for the incidence or severity of AEs reported during this study. The AEs reported were consistent with the safety results from previous clinical studies and no risks were identified during this study.

No relevant trends over time and between treatment groups were observed in mean and median values for urinalysis, hematology or chemistry safety tests. Abnormal values were reported for a few subjects, but none were considered clinically significant by the principal investigator. No clinically significant post-dose abnormalities related to vital signs, physical examinations, or vision changes were reported during this study.