Clinical Study Report Synopsis

Drug Substance	Selumetinib
Study Code	D1532C00069
Edition Number	1
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A Phase I, Randomized, Open-label, Single-center, Crossover Study to Assess the Effect of Food on the Pharmacokinetics of a 75 mg Single Oral Dose of Selumetinib in Healthy Male Volunteers Aged 18 to 45 Years

Study dates: First subject enrolled: 13 November 2013
Last subject last visit: 16 February 2014

Phase of development: Clinical pharmacology (I)

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

Publications

Not applicable.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	Type	Description	Description
Primary	Pharmacokinetic	To investigate the effect of food, in comparison to fasting conditions, on the exposure of selumetinib after a single 75 mg dose in healthy volunteers.	C_{max}, AUC, $AUC_{(0-t)}$ determined from selumetinib fed and fasted plasma concentration data.
Secondary	Pharmacokinetic	To investigate the PK of selumetinib under fed and fasting conditions. To investigate the PK of N-desmethyl selumetinib under fed and fasting conditions.	t_{max}, $AUC_{(0-12)}$, λ_z, $t_{½}$, CL/F, V_{ss}/F, V_z/F, and MRT for selumetinib and AUC, C_{max}, t_{max}, λ_z, $t_{½}$, MRT, $AUC_{(0-12)}$, and $AUC_{(0-t)}$ for the N-desmethyl metabolite. MR_{AUC}, $MRAUC_{(0-t)}$, and MRC_{max}.
	Safety	To further assess the safety and tolerability of selumetinib by assessment of adverse events (AEs), laboratory variables, 12-lead electrocardiogram (ECGs), and vital signs.	AEs, laboratory variables, vital signs, physical examination, and 12-lead ECG.

AE: Adverse event; AUC: Area under plasma concentration-time curve; $AUC_{(0-t)}$: Area under plasma concentration-time curve from time zero (predose) to the last quantifiable concentration; $AUC_{(0-12)}$: Area under the plasma concentration-time curve from time zero to 12 hours postdose; C_{max}: Maximum observed concentration in plasma; CL/F: Apparent systemic plasma clearance; CSP: Clinical study protocol; ECG: electrocardiogram; MR: Metabolite to parent ratio; MRT: Mean residence time; t_{max}: Time to C_{max}; λ_z: Terminal rate constant; $t_{½}$: Apparent terminal half-life; V_{ss}/F: Apparent volume of distribution equilibrium; V_z/F: Apparent volume at distribution associated with the terminal phase

Study design

This was as a Phase I, open-label, randomized, single-center, 2-period crossover study in healthy male volunteers in order to investigate the effect of food on the PK of a single dose of selumetinib 75 mg.

The study consisted of 4 visits. Visit 1 was screening evaluations and took place within 28 days of Visit 2. Visits 2 and 3 were treatment visits and the healthy volunteers were resident at the study center from Day -1 until Day 3 for both visits. Healthy volunteers were

randomized to 1 of 2 treatment sequences on Day 1 of Visit 2 and received selumetinib on Day 1 of both Visit 2 and Visit 3:

- Sequence 1: 75 mg selumetinib oral dose in a fasted state (Treatment A) followed by a second 75 mg selumetinib oral dose in the fed state (Treatment B) with a washout period of at least 7 days between investigational product administrations

- Sequence 2: 75 mg selumetinib oral dose in the fed state (Treatment B) followed by a second 75 mg selumetinib oral dose in the fasted state (Treatment A) with a washout period of at least 7 days between investigational product administrations

Visit 4 was the follow-up visit and took place 7 to 10 days after discharge from Visit 3.

For Treatment A, selumetinib in the fasted state, healthy volunteers received a single oral dose of 75 mg selumetinib after fasting overnight for at least 10 hours and remained fasted until 4 hours postdose. No water was allowed from 1 hour before administration until 1 hour after administration, except for water required to swallow the selumetinib capsules.

For Treatment B, selumetinib in the fed state, healthy volunteers received a high fat breakfast in accordance with the Food and Drug Administration (FDA) guidance 2002, after fasting overnight for at least 9.5 hours. The entire high fat meal was consumed within 30 minutes and a single oral dose of 75 mg selumetinib was administered 30 minutes after the start of the high fat breakfast. Healthy volunteers fasted for at least 4 hours postdose. No water was allowed from 1 hour before administration until 1 hour after administration, except for water required to swallow the selumetinib capsules. The high fat breakfast had a total of approximately 800 to 1000 calories with approximately 50% of the calorific content made up from fat. The meal derived approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat respectively.

Other than the high fat breakfast for Treatment B, all other meals and snacks were standardized and provided at the same time in each treatment period (Visits 2 and 3).

Target subject population and sample size

Up to 34 healthy male volunteers aged 18 to 45 years (inclusive) who 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) were included in the study.

A total of 34 healthy volunteers were randomized and all 34 received the treatment and 32 completed the study.

Investigational product: dosage, mode of administration and batch numbers

Table S2 Details of 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	Lot ID: 45190.1

Selumetinib capsules were packaged in high-density polyethylene (HDPE) bottles containing 60 capsules per bottle.

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

Duration of treatment

Each healthy volunteer received a single dose of selumetinib in 2 different ways.

The study consisted of screening 28 days prior to administration of the first dose of the investigational product. Visits 2 and 3 were the treatment visits, each separated by a washout period of at least 7 days between investigational product administrations. The follow-up procedures were performed for 7 to 10 days after discharge from Visit 3.

Statistical methods

Following log-transformation, C_{max}, AUC, and $AUC_{(0-t)}$ of selumetinib and N-desmethyl selumetinib were separately analyzed using a linear mixed-effects analysis of variance model. Transformed back from the logarithmic scale, geometric least-squares means together with confidence intervals ([CIs] 2-sided 95%) for C_{max}, AUC, and $AUC_{(0-t)}$ were estimated and presented. Also, ratios of geometric least squares means (fed/fasted) together with CIs (2-sided 90%) was estimated and presented.

An analysis of selumetinib and N-desmethyl selumetinib t_{max} using the Wilcoxon Signed Rank Test, and the Lehman median estimator of difference (fed-fasted) and 90% CIs was also be presented.

The food effect analyses only included healthy volunteers that had evaluable pharmacokinetic data in both study periods.

Concentrations for the selumetinib amide metabolite were determined and reported by the bioanalysis laboratory, with the results included in a concentration listing only.

The adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) 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 listings of data for frequency and severity of AEs and results of clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations were presented by treatment. The safety data was presented by treatment and included all healthy volunteers who received at least one dose of investigational product administration. For clinical laboratory tests, listings of values for each healthy volunteer will be presented with abnormal or out of range values flagged.

Subject population

A total of 34 healthy male volunteers were randomized and all the volunteers received the investigational product as per the randomization scheme. Two healthy volunteers (E001067 and E001088), completed the treatment however discontinued from the study and were lost to follow-up.

The age of male volunteers ranged from 19 to 44 years (mean age of 27 years) and the BMI from 20.38 to 29.88 kg/m^2 (mean BMI of 25.39 kg/m^2), and weight ranged from 60.0 kg to 97.2 kg, in accordance with the inclusion criteria.

Summary of pharmacokinetic results

Administration of selumetinib 75 mg after a high-fat, high-calorie meal lowered both selumetinib and N-desmethyl selumetinib C_{max} and delayed t_{max} compared to administration in a fasted state.

Table S3 Statistical comparison of selumetinib key plasma pharmacokinetic parameters

Analyte	Parameter (units)	Treatment	N	Geometric LS Mean	Ratio (%)	90% CI
Selumetinib	AUC (ng·h/mL)	Fasted	34	4156		
		Fed	34	3495	84.08	(80.72, 87.59)
	$AUC_{(0-t)}$ (ng·h/mL)	Fasted	34	4104		
		Fed	34	3438	83.76	(80.31, 87.35)
	C_{max} (ng/mL)	Fasted	34	1428		
		Fed	34	710.6	49.76	(43.82, 56.51)
N-desmethyl selumetinib	AUC (ng·h/mL)	Fasted	29	325.7		
		Fed	29	281.6	86.46	(82.72, 90.38)
	$AUC_{(0-t)}$ (ng·h/mL)	Fasted	34	276.4		
		Fed	34	239.0	86.47	(82.67, 90.46)
	C_{max} (ng/mL)	Fasted	34	93.40		
		Fed	34	49.26	52.74	(45.88, 60.64)

CI: Confidence interval; LS: Least squares
Results based on linear mixed-effects model with sequence, period, and treatment as fixed effects and volunteer nested within sequence as a random effect.
Fasted Treatment A: TC-5214 following a 10-hour fast;
Fed Treatment B: TC-5214 30 minutes after the start of a high-fat, high-calorie breakfast.

The geometric LS mean ratios for AUC and $AUC_{(0-t)}$ for both analytes were below 100%, with an approximate 16% reduction in total exposure. The lower 90% CI limits for AUC and $AUC_{(0-t)}$ for both analytes were above 80%.

A statistical comparison of t_{max} was also conducted (Table 11.2.6) indicating food prolongs the time to maximum plasma concentrations. The median difference (90% CI) for selumetinib was 1.49 (1.00, 1.75) hours, and for N-desmethyl selumetinib was 1.25 (1.00, 1.99) hours.

Elimination was unaffected by food. For selumetinib the arithmetic mean (range) $t_{1/2}$ values were similar between both the fed (7.97 hours [3.98 to 14.4 hours]) and fasted state (8.33 hours [5.80 to 12.1 hours]). For N-desmethyl selumetinib the arithmetic mean (range) $t_{1/2}$ values were similar between in both the fed (7.04 hours [3.14 to 14.0 hours]) and fasted state (7.76 hours [2.97 to 16.4 hours]).

Food administration affected both the parent and metabolite to the same extent with metabolite to parent ratios for both AUC and C_{max} similar across treatments.

Summary of safety results

- There were no deaths, SAEs, or AEs leading to discontinuation of the investigational product reported in this study

- Overall, 15 healthy volunteers (44.1%) reported at least 1 AE. The number of volunteers reporting at least 1 AE was higher in Treatment A (9 [26.5%)] healthy volunteers) than in Treatment B (6 [17.6%] healthy volunteers)

- The most commonly reported AEs were upper respiratory tract infection reported by 2 (5.9%) healthy volunteers after receiving Treatment A and 1 (2.9%) healthy volunteer after receiving Treatment B; increased aspartate aminotransferase (AST) was reported by 3 healthy volunteers after receiving Treatment A, none of which were attributed to investigational product

- Of the 15 healthy volunteers who reported at least 1 AE, 8 AEs were not resolved at the time of the last visit in 6 healthy volunteers who either received Treatment A or Treatment B. Volunteer E001029 in Treatment A had elevated AST which was ongoing and no action was taken with regard to the investigational product. Similarly, Volunteer E001048 in Treatment A had elevated AST and ALT which was ongoing and there was no action taken with respect to the investigational product

- All AEs reported in the study were mild except for increased blood creatinine phosphokinase (CPK) considered as severe in 2 volunteers:

  – Volunteer E001029: The volunteer was dosed on 21 January 2014 at 0815 and had no CPK elevations during the inpatient stay. On 30 January 2014, during the follow-up visit, the CPK was 72.89 ukat/L which was following strenuous physical activities over 3 continuous days from 28 January 2014 to 30 January 2014. There was raised AST (103 U/L) and normal ALT observed on the same day. The volunteers denied any fatigue, myalgia or urinary problems. On 02 February 2014 at 0831 the CPK was 1,179ukat/L and AST was 73 U/L. The volunteer was clinically stable and did not return to clinic for additional CPK. On 19 February 2014, the AE was closed as unknown outcome, and not related to the investigational product.

  – Volunteer E001048: The volunteer was a 28-year old male who had no CPK elevation during his inpatient stay. The volunteer was dosed on 21 January 2014 at 0845 with 75 mg of the investigational product. On 30 January 2014, during the follow-up visit, the volunteer's CPK value was 163.04 ukat/L following regular strenuous physical activities which included fast sprints, 100 push-ups and 150-pound bench press from 24 January 2014 to 28 January 2014. There was also concurrent elevations of AST (301 U/L) and ALT (97 U/L). The volunteer was

followed on 10 February 2014 after the study closure where the AST (37U/L) and ALT (48U/L) were back to normal. The CPK had been inadvertently missed in these repeat biochemistry tests and the volunteer would not return for further tests.

- The majority of AEs were considered to be not related to the investigational product. Two volunteers reported AEs considered to be related to the investigational product administration: Volunteer E001046 (decreased appetite, diarrhoea, nausea) and Volunteer E001011 (nausea, vasodilation)

- Variation, with no trend over time and between treatments, was observed in the laboratory variables. Although a number of abnormal values were reported, none of the abnormal laboratory values were considered to be clinically significant by the investigator

- Variation, but no relevant trends, over time and between treatments were observed in the vital signs measurements. No clinically important changes in vital signs were recorded

- Abnormal 12-lead ECG readings, were reported, but none were considered to be clinically significant and were not reported as AEs. No urinalysis were reported in the study

- Clinically significant abnormal physical examination findings were reported in 3 healthy volunteers and all were reported as AEs which were mild in severity:

  – Volunteer E001002 (follow-up visit; Treatment B): system “Head, eyes, ears, nose and throat (HEENT)” was reported as a mild upper respiratory tract infection, considered to be not related to the investigational product by the investigator

  – Volunteer E001028 (Day 3 and follow-up visit; Treatment B): system “skin on right forearm” was reported as a ecchymosis of Right forearm due to venipuncture, considered to be not related to the investigational product by the investigator

  – Volunteer E001076 (Day 3 and follow-up visit; Treatment A): “skin” was reported as superficial Thrombophlebitis left antecubital fossa with palpable cord but no erythema, considered to be not related to the investigational product by the investigator