Clinical Study Report Synopsis

Drug Substance	AZD6244
Study Code	D1532C00077
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A Phase I, Single-centre, Non-randomised, Open-label, Pharmacokinetic and Mass Balance Study of Orally Administered [^{14}C]-selumetinib in Healthy Male Volunteers

Study dates: First subject enrolled: 18 October 2013
Last subject last visit: 22 November 2013

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 centre

This study was conducted at 1 study centre in the United Kingdom (UK), Quotient Clinical Limited, Mere Way, Ruddington Fields, Nottingham, NG11 6JS, under the direction of Dr. Stuart Mair.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	PK	To determine the rates and routes of excretion of [^{14}C] radiolabeled selumetinib in healthy volunteers by assessment of concentrations of total [^{14}C] radioactivity of selumetinib and N-desmethyl selumetinib in plasma and percent recovery of radioactive dose in urine and faeces.	Amount of [^{14}C] radioactivity in plasma and whole blood and the resulting AUC, $AUC_{(0-t)}$, $AUC_{(0-12)}$, C_{max}, t_{max}, $t_{½}$, CL/F, V_z/F, and V_{ss}/F were determined. Amount and percentage of radioactive dose recovered in both urine and faeces were calculated
Secondary	PK	To provide samples for subsequent analyses to characterise the metabolism of [^{14}C]-selumetinib through the assessment of metabolic profiles of selected plasma and excreta samples.	Identification and quantification of metabolites in plasma and excreta have been reported separately from the CSR.
Secondary	PK	To calculate the PK parameters of selumetinib and N-desmethyl selumetinib in plasma and PK parameters of total plasma radioactivity.	Selumetinib and N-desmethyl selumetinib plasma concentrations and the resulting AUC, $AUC_{(0-t)}$, $AUC_{(0-12)}$, C_{max}, t_{max}, $t_{½}$, and selumetinib CL/F, V_z/F, and V_{ss}/F as well as plasma N-desmethyl selumetinib to selumetinib ratios for AUC and C_{max} were determined
Secondary	PK	To compare disposition of drug related total radioactivity in whole blood to plasma	Whole blood to plasma [^{14}C] radioactivity ratios for concentrations and selected PK parameters (AUC and C_{max}) were determined.
Secondary	Safety	To evaluate the safety and tolerability of a single dose of selumetinib.	AEs, vital signs, ECG, haematology, clinical chemistry, urinalysis, physical examination, LVEF, and ophthalmology assessments

AE: Adverse event; AUC: Area under the concentration-time curve from zero to infinity, $AUC_{(0-t)}$: Area under the concentration-time curve from zero to the last measurable concentration; $AUC_{(0-12)}$: Area under the concentration-time curve from zero to 12 hours postdose; CL/F: Apparent oral clearance; C_{max}: Maximum observed concentration; CSR: Clinical study report; ECG: Electrocardiogram; LVEF: Left ventricular ejection fraction; PK: Pharmacokinetic; $t_{1/2}$: Elimination half-life; t_{max}: Time of C_{max}; Vss/F: Apparent volume of distribution at equilibrium; V_z/F: Apparent volume of distribution

Study design

This was a phase 1, open label, single dose study to determine the rates and routes of elimination of a single dose of [^{14}C]-selumetinib and its metabolites by assessment of concentrations of total [^{14}C] radioactivity in blood and plasma, concentrations of selumetinib

and N-desmethyl selumetinib in plasma and percent recovery of the radioactive dose in urine and faeces.

A total of 6 healthy male volunteers, aged 50 to 65 years (inclusive), were recruited at 1 study centre.

Healthy volunteers were screened over a period of maximum 28 days for eligibility. Screening assessments included evaluation of clinical chemistry, haematology, urinalysis, a physical examination, vital signs, an echocardiogram, a full ophthalmological examination and paper electrocardiogram (ECG). Study-related procedures were only performed after signing of the informed consent form (ICF).

Eligible healthy volunteers were admitted to the study centre on Day -1.

Healthy male volunteers received a single dose of [^{14}C]-selumetinib Hyd-Sulfate administered as 3 x 25 mg oral capsules on Day 1. Healthy volunteers were scheduled to remain at the study centre up to 7 days following receipt of the investigational product when samples of blood, urine, and faeces were collected. The length of the residential period was extended based on emerging data. Once the mass balance cumulative recovery >90% was achieved or <1% of the dose administered was collected in urine and faeces within 2 consecutive days, healthy volunteers were permitted to leave the study centre.

When emerging data indicated that adequate dose recovery was not achieved after 7 days, the healthy volunteers were asked to continue urine and/or faecal collections for a further 3 days on an inpatient basis. If adequate dose recovery was still not achieved, the healthy volunteers were asked to return to the study centre approximately 7 days later, for a further 24-hour collection. For these healthy volunteers, a final follow-up visit took place on the last day of urine and/or faecal collection.

Target subject population and sample size

It was estimated that 6 healthy male volunteers were sufficient to provide a reliable estimate of rates and routes of excretion.

A total of 6 healthy adult male volunteers were enrolled into 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	Oral capsules 25 mg (free base equivalent) selumetinib Hyd Sulfate capsule containing 7.52 MBq (203.3 μCi) [^{14}C]-selumetinib	Quotient Clinical Ltd	115579/C/01

Duration of treatment

Healthy volunteers received a single administration of [^{14}C]-selumetinib on Day 1.

The treatment period of the study, excluding the screening period, was of a total duration of up to 3 weeks.

Statistical methods

No formal statistical hypothesis testing was performed in this study. The statistical analysis was descriptive and consisted of subject listings, graphs, and summary statistics comprising arithmetic mean, standard deviation (SD), median, minimum, maximum, geometric mean, and/or geometric coefficient of variation as appropriate.

Subject population

A total of 6 healthy adult male volunteers with a mean age of 56 years ranging from 52 to 61 years and a mean body mass index (BMI) of 27.2 kg/m^2 were enrolled in the study. All the 6 volunteers received 75 mg (3 x 25 mg) [^{14}C]-selumetinib Hyd-Sulfate oral capsules as a single dose per the protocol and completed the study.

Summary of pharmacokinetic results

Table S3 summarises the cumulative total amount of radioactivity and percent of radioactive dose recovered.

Approximately 33% of the radioactive dose was recovered in urine, most of which during the first 48 hours postdose. Approximately 59% of the radioactive dose was recovered in faeces, most of which during the first 120 hours postdose. When combined, approximately 93% of the radioactive dose was recovered.

Plasma radioactivity samples were limited (see bioanalytical report for details). Therefore, plasma total radioactivity parameters and associated parameters were considered unreliable. However, time-matched plasma selumetinib, plasma N-desmethyl selumetinib, and whole blood total radioactivity to plasma total radioactivity concentration ratios were calculated.

Plasma and whole blood total radioactivity declined slower than selumetinib and N-desmethyl selumetinib. Therefore, plasma selumetinib and N-desmethyl selumetinib to plasma total radioactivity ratios were approximately 54% and 4%, respectively, and decreased with time. Ratios were not determined at 72 hours and 48 hours and 72 hours, respectively, as selumetinib and N-desmethyl selumetinib were not quantifiable.

Whole blood to plasma concentration ratios ranged from 60% to 70% and did not appear to change with time.

Table S3 Summary of total radioactivity recovery parameters

Parameter	Statistic	Urine (N=6)	Faecal (N=5)	Total (N=5)
CumAe (mg)	Geometric mean	23.1	40.9	64.9
	GCV%	23.6	19.7	1.2
	Min, Max	17.2, 34.7	29.1, 47.8	63.8, 65.9
CumFe (%)	Geometric mean	33.0	58.5	92.8
	GCV%	23.5	19.6	1.2
	Min, Max	24.9, 49.6	41.7, 68.3	91.2, 94.2

Parameters determined from collections up to 216 hours postdose. CumAe cumulative amount recovered; CumFe Cumulative percent of dose recovered; GCV% Geometric coefficient of variation; Min Minimum; Max Maximum.

Summary of safety results

- A single dose of selumetinib administered orally was found to be safe and well-tolerated in healthy male subjects
- No deaths, SAEs, and DAEs were reported in the study
- All the AEs reported were mild in intensity and assessed by the Investigator as not related to the investigational product. All the AEs resolved
- No clinically significant abnormalities were reported in the laboratory assessments, vital signs, ECG and physical examination