AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Cediranib (AZD2171)
Study Code	D8480C00046
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An Open-Label, Phase II Study to Evaluate the Biological Activity of AZD2171 (cediranib, RECENTIN™), as Measured by FDG-PET Response, in Patients with Metastatic Gastro-Intestinal Stromal Tumours (GIST) Resistant or Intolerant to Imatinib Mesylate

Study dates:

First subject enrolled: 25 September 2006
Last subject enrolled: 31 January 2008
Analysis data cut-off: 8 July 2009 (study ongoing)

Phase of development:

Therapeutic exploratory (II)

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

This study is ongoing: 3 patients (all with soft tissue sarcoma [STS]) remained in the study at the data cut-off date of 8 July 2009. As this is an uncontrolled study in an unrelated indication for which marketing approval is not currently being sought, a synopsis-style clinical study report (CSR) was considered sufficient.

Study centre(s)

This was a 2 centre, UK-based study conducted at London and Manchester.

Publications

Gardner K, Judson I, Leahy M, Barquin E, Marotti M, Collins B et al. Activity of cediranib, a highly potent and selective VEGF signalling inhibitor, in alveolar soft part sarcoma. J Clin Oncol 2009;27:15 suppl. Abstract 10523.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
Determine the preliminary anti-tumour activity of AZD2171 (cediranib, 45 mg/day) in GIST patients by assessment with FDG-PET following 8 days and 4 weeks of dosing (central review of SUV_{max})	SUV_{max} 8 days and 4 weeks after dosing (central review)
Secondary	**Secondary**
Determine the preliminary anti-tumour activity of cediranib (45 mg/day) in GIST patients by FDG-PET following 8 days and 4 weeks of dosing (investigator review of SUV_{max})	SUV_{max} 8 days and 4 weeks after dosing (investigator review)
Determine the efficacy of cediranib (45 mg/day) in GIST and STS patients by objective tumour response (RECIST) determined by site	Objective tumour response (RECIST) at Week 8, Week 16, and every 12 weeks thereafter (investigator review)[a]
Determine the anti-tumour activity of cediranib (45 mg/day) in GIST patients by central review of CT images for a range of CT assessments	Central review of CT assessments at Week 8, Week 16, and every 12 weeks thereafter including: objective tumour response (RECIST)[a], major axis (axial plane), total lesion volume
Determine the anti-tumour activity of cediranib (45 mg/day) in GIST patients from central review of FDG-PET images for a range of endpoints	Central review of FDG-PET images at Day 8 and Day 29 to assess: total lesion volume, metabolic volume, average metabolic region SUV, SUV_{max} (pixel), SUV_{max} (1 cm)
Compare intra-patient $C_{ss,min}$ values for GIST and STS patients who receive long-term therapy with cediranib	$C_{ss,min}$ values in GIST and STS patients
Investigate if plasma exposure of cediranib at 45 mg/day in GIST patients is less than in patients with other solid tumours treated at the same dose and schedule (from historical data)	$C_{ss,min}$, $C_{ss,max}$, AUC_{ss} and t_{max} in GIST patients

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Investigate safety and tolerability of cediranib in GIST and STS patients	Adverse events, clinical laboratory findings, electrocardiogram and vital signs in GIST and STS
Exploratory[b]	
To investigate the effect of cediranib on the surrogate biomarkers of c-kit (a proto-oncogene that encodes the transmembrane tyrosine kinase receptor CD 117), VEGF and sVEGFR-2 measured in the blood of GIST patients.	c-kit, VEGF and sVEGFR-2
To investigate the relationship between the change from baseline in SUV_{max} and the multiple dose PK parameters of $C_{ss,min}$, $C_{ss,max}$ and AUC_{ss} in GIST patients.	Relationship between SUV_{max} and $C_{ss,min}$, $C_{ss,max}$ and AUC_{ss} in GIST patients

[a] Best objective tumour response is presented in this synopsis.
[b] There were 6 additional exploratory objectives included in the protocol which are not reported in this synopsis.

AUC_{ss} Area under the plasma concentration-time curve during any dosing interval at steady state; $C_{ss,max}$ Maximum (peak) steady state drug concentration in plasma during dosing interval; $C_{ss,min}$ Minimum (trough) steady state drug concentration in plasma during dosing interval; CT Computed tomography; FDG-PET 2-[F-18]-fluoro-2-deoxy-D-glucose positron emission tomography; GIST Gastro-intestinal stromal tumour; PK Pharmacokinetic; RECIST Response evaluation criteria in solid tumours; SUV_{max} Maximum standardised uptake value; STS soft tissue sarcoma; sVEGFR-2 Soluble VEGF receptor 2; t_{max} Time to reach peak or maximum concentration or maximum response following drug administration; VEGF Vascular endothelial growth factor.

Study design

This was a phase II, open-label study to evaluate the preliminary anti-tumour activity of cediranib (45 mg/day) in patients with gastro-intestinal stromal tumour (GIST). 2-[F-18]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) was used to assess tumour metabolic activity in GIST patients after dosing on Day 8 and Day 29. The potential efficacy of cediranib after longer term treatment was examined by comparing objective response rates (response evaluation criteria in solid tumours [RECIST]) and tumour size in GIST and STS patients.

The protocol included an option to include a cohort to receive cediranib 60 mg and this option was not taken.

Target subject population and sample size

Approximately 35 male or female patients (25 patients with GIST and 10 patients with STS) aged ≥18 years old were to be recruited. Histological or cytological confirmation of GIST (that was resistant or intolerant to imatinib mesylate) or metastatic STS (that was refractory to standard therapies or for which no standard therapy existed) was required for inclusion in the study. Patients must have had a World Health Organisation (WHO) performance status (PS) between 0 to 2, a life expectancy of >12 weeks and measurable disease according to RECIST guidelines.

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

Cediranib study medication was manufactured and supplied by AstraZeneca as beige, round, film-coated tablets at 15 mg (formulation number F013341, batches 32752A05, 40507A06 and 52451E07), 20 mg (formulation number F013343, batches 33688B05 and 42364D08) and 30 mg (formulation number F013345, batches 32757H05, 52454G07 and 40508I06). A 15 mg tablet and a 30 mg tablet were administered to achieve the 45 mg dose. The 20 mg tablets were provided to patients requiring a dose reduction for management of toxicity.

Cediranib was to be taken at least 1 h prior to the consumption of a meal or more than 2 h after a meal was ingested. Patients were instructed to take cediranib at approximately the same time each day (preferably in the morning).

Duration of treatment

Patients continued taking their oral, once daily dose of cediranib indefinitely, assuming they did not meet the criteria for discontinuation, were free from intolerable toxicity and in the investigators opinion were receiving some benefit from the treatment.

Statistical methods

The protocol-defined primary analysis at 16 weeks was performed for FDG-PET data and RECIST data (up to Week 16).

The statistical analysis was conducted on SUV_{max} from the central and investigator reviews for GIST patients who had scans with readable results at baseline and the time point analysed (Day 8 or Day 29). A paired t-test was applied to compare readable results at Day 8 and Day 29 to readable baseline results.

Using the same statistical method, sensitivity analyses of SUV_{max} from the central and investigator reviews were conducted for GIST patients who received consecutive once daily doses for the first week (7 days) of treatment and then 75% of the planned consecutive daily doses for the following 3 weeks of treatment to assess the differences in the readable results between post-dosing (at Day 8 and Day 29) and baseline.

Objective tumour response (RECIST) was summarised and plotted.

Descriptive statistics and plots were produced for the biomarker variables and pharmacokinetic (PK) data.

All safety data were listed and summarised descriptively.

Subject population

Thirty-six patients were enrolled in the study, 35 entered the study and 34 received treatment (24 GIST and 10 STS patients). Note: 1 of the 2 patients who were enrolled but did not receive cediranib was given a patient number and is therefore included in the N number of the

full analysis set (FAS) but has no data. In total, 33 of the 36 patients enrolled had discontinued from the study at the time of the data cut-off of 8 July 2009 (26 GIST [including the patient who did not receive treatment but was given a patient number] and 7 STS patients); 21 due to worsening of the condition under study, 9 due to an adverse event (AE), 2 due to incorrect enrolment and 1 due to death (GIST patient: AE of tumour haemorrhage [liver] which led to death).

The median ages of GIST and STS patients were 56.1 years (range 37 to 73 years) and 44.6 years (range 27 to 57 years) respectively; 17/25 GIST patients (68%) and 4/10 STS patients (40%) were male. Demographics were representative of the GIST and STS patient populations.

All GIST patients who received cediranib had been given imatinib and 13/25 GIST patients (52%) had also been given sunitinib as a second line therapy. Seven of the 25 GIST patients (28%) had a WHO PS of 0, 16/25 (64%) had a WHO PS of 1 and 1/25 (4%) had a WHO PS of 2. The most common primary tumour locations for GIST patients were small bowel (9/25 [36%]) and stomach (8/25 [32%]). The predominant site of metastatic/locally advanced disease in GIST patients was hepatic (including gall bladder) (20/25 [80%]). Nineteen of the 25 GIST patients (76%) had received prior surgery.

Four of the 10 STS patients (40%) had received prior chemotherapy. Two STS patients (20%) had a WHO PS of 0 and 8 (80%) had a WHO PS of 1. The predominant site of metastatic/locally advanced disease in STS patients was respiratory (9 patients [90%]). All STS patients had received prior surgery. Six of the 10 STS patients (60%) had alveolar soft part sarcoma (ASPS). This is a rare entity making up <1% of STSs and is therefore over-represented in this study.

Three STS patients (all ASPS) were ongoing in the study at the time of data cut-off.

Summary of efficacy results

There was no significant decrease from baseline in SUV_{max} at Day 8 or Day 29 in GIST patients following central review averaged across the studied population. Investigator review of the data was consistent with central review.

Table S2 Change in SUV_{max} from baseline to Day 8 and Day 29 in GIST patients: Central Review (Evaluable for safety [EFS] – evaluable for SUV_{max})

Comparison	n	Mean difference	Paired t-value[a]	95% CI	p-value[a]
SUV_{max} (Day 8) – SUV_{max} (baseline)	22	-0.515	-1.115	-1.480, 0.450	0.278
SUV_{max} (Day 29) – SUV_{max} (baseline)	20	-0.172	-0.297	-1.380, 1.040	0.770

[a] The paired t-value and p-value are based on the paired t-test method.

Table S3 Summary of % change from baseline in SUV_{max} in GIST patients: Central Review (EFS - evaluable for SUV_{max})

Comparison of SUV_{max}	n	Median % change	Arithmetic mean % change	Geometric mean % change[a]	95% confidence interval for mean
Day 8 vs baseline	22	-11.62	6.795	-1.347	-19.950, 33.540
Day 29 vs baseline	20	9.36	4.644	1.210	-8.050, 17.340

[a] Geometric means in % change were calculated as 100 x (exp(mean of log(post-baseline/baseline))-1).

The sensitivity analysis results were consistent with the results for GIST patients who provided evaluable SUV_{max} data.

The scatter plot showed substantial agreement between investigator and central review for % change in SUV_{max} assessments.

There was evidence of activity in some GIST patients by FDG-PET with confirmed decreases in SUV_{max} (tumour averaged percentage decrease relative to baseline) at Day 8 and Day 29 ≥10% (n=5) and 4 partial metabolic responses (≥ 25% decrease) by Day 29 with 2 partial metabolic responses at Day 8 and Day 29 (confirmed).

There was no relationship demonstrated between best % change in tumour averaged SUV_{max} and prior treatment.

Central and investigator reviews of RECIST response were similar in GIST patients. Although there were no complete responses or partial responses (PRs) in GIST patients, 14 of the 15 GIST patients with stable disease (SD) had SD recorded ≥112 days (16 weeks) (investigator review). In resistant GIST, 3 month SD is deemed clinically meaningful.

There was no relationship between confirmed metabolic response on FDG-PET and SD ≥112 days by RECIST in this study.

Four STS patients had PRs according to investigator review.

There was a strong evidence of activity by objective response in ASPS: 4/6 ASPS patients had a confirmed PR with their responses being durable (duration of response being 241 days, 247 days, 365 days and 633 days). The other 2 ASPS patients had SD, with SD scans up to 57 days and 449 days (investigator review).

Summarising data according to prior sunitinib treatment showed no differences between patients pre-treated with sunitinib and patients not pre-treated with sunitinib.

For all CT parameters, the mean level at Week 8 (57 days) and Week 16 (113 days) was greater than the corresponding baseline mean level in GIST patients. For the secondary outcome variables considered most clinically relevant, major axis (axial plane) and total lesion volume, this increase was not statistically significant.

There were no consistent trends in changes from baseline to Day 8 or Day 29 on FDG-PET measures including total lesion volume, metabolic volume, average metabolic region SUV, SUV_{max} (Pixel) and SUV_{max} (1 cm) in GIST patients (central review).

Summary of pharmacokinetic results

Limited PK results were available as many patients had insufficient information (such as dose time/sample time) collected to enable appropriate determination of PK parameters. This was specific to collection of information related to the PK samples, therefore only PK was affected. There were insufficient data to draw meaningful conclusions regarding intra-patient $C_{ss,min}$ values for patients who received long-term therapy.

Steady state plasma exposure values of cediranib 45 mg in GIST patients were similar to values observed for steady state cediranib 45 mg in previous studies in patients with other solid tumour types (D8480C00001 and D8480C00023).

Based on the available data from this study, there was no relationship between the change from baseline in SUV_{max} and multiple dose PK parameters in GIST patients.

Summary of pharmacodynamic results

Vascular endothelial growth factor-A (VEGF) levels increased on treatment with cediranib from the earliest time point measured and stayed above baseline. Soluble vascular endothelial growth factor receptor 2 (sVEGFR-2) levels decreased over time. Changes seen in VEGF and sVEGFR-2 are in line with observations in other studies with cediranib. c-kit levels did not show consistent trends in change over time on treatment with cediranib.

Summary of safety results

The overall and first 12 weeks mean average daily dose was 34.4 mg and 32.5 mg for GIST patients and 31.4 mg and 30.0 mg for STS patients.

In total, 21/24 GIST patients (87.5%) and 7/10 STS patients (70%) required a dose reduction or pause. Dose reductions were required by 18/24 GIST patients (75%) and 5/10 STS patients

(50%). Dose pauses were required by 18/24 GIST patients (75%) and 7/10 STS patients (70%). The majority of patients had a dose reduction and/or dose pause for management of toxicity during the study. Fifty percent of all patients had a dose reduction or pause in the first 40 days, a possible reason for the lower average daily dose observed in the first 12 weeks than overall. The mean could also be influenced by a small number of patients continuing for a long period of time beyond the 12 weeks.

All patients experienced an AE during the study. The most common AEs were diarrhoea (21 GIST patients [87.5%], 8 STS patients [80%]), fatigue (18 GIST patients [75%], 7 STS patients [70%]), hypertension (19 GIST patients [79.2%] 4 STS patients [40%]) and decreased appetite (13 GIST patients [54.2%] and 4 STS patients [40%]). AEs of CTC grade ≥3 with a total frequency ≥10% were fatigue, hypertension and diarrhoea. One GIST patient had grade 4 hypertensive crisis and 1 GIST patient had grade 5 hepatic haemorrhage (the site of metastatic disease).

In total, 2 patients died during the study: 1 STS patient died as a result of disease under investigation (neoplasm malignant) and 1 GIST patient died as a result of an AE with the outcome death (grade 5 hepatic haemorrhage, mentioned above) that was also recorded as a death due to the disease under investigation (tumour haemorrhage).

Ten GIST patients (41.7%) and 3 STS patients (30%) had a serious adverse event (SAE). The only SAE reported by more than 1 patient was abdominal pain which was reported by 1 GIST patient and 1 STS patient.

Seven GIST patients (29.17%) and 4 STS patients (40%) had investigational product discontinued due to an AE. The most common AEs leading to discontinuation were fatigue (4 GIST patients [16.67%], 0 STS patients) and hypertension (1 GIST patient [4.17%], 1 STS patient [10%]).

The trends in laboratory and vital signs data were consistent with data from other cediranib studies. One patient showed liver enzymes and total bilirubin elevation and recovered after study drug discontinuation without sequels. Proteinuria >++ was reported in 2/16 GIST patients and 3/9 STS patients.

Conclusion(s)