AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Cediranib (AZD2171)
Study Code	D8480C00014
Edition Number	1
Date	07 September 2009

A Phase I, Open-Label Study to Assess the Safety, Tolerability and Pharmacokinetics of Daily Oral Doses of cediranib (RECENTIN™; AZD2171) (20, 30 or 45 mg) when Co-administered with Daily Oral Doses of AZD0530 (125 mg or 175 mg) in Patients with Advanced Solid Tumours.

Study dates:	First patient enrolled: 3 May 2007 Last patient completed: 27 October 2008 (cut-off date for report)
Phase of development:	Clinical pharmacology (I)

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

Study centres

This was a multi-centre study conducted at 3 centres in Germany.

Publications

Trarbach T, Drevs J, Strumberg D, Gauler TC, Schneider V, Eberhardt WE, et al. A Phase I, open-label, multicenter study of cediranib and AZD0530 in patients with advanced solid tumours. J Clin Oncol, 2008 ASCO Annual Meeting Proc Vol 26, No 15S (May 20 Suppl):3592.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
To determine the safety and tolerability of ascending daily oral doses of cediranib (20, 30 or 45 mg) when co-administered with daily oral doses of AZD0530 (125 mg or 175 mg), to patients with advanced solid tumours by assessment of AEs, vital signs, pulmonary function tests superseded by high resolution CT scans, clinical chemistry, haematology, urinalysis, ECG and physical examination.	AEs, clinical chemistry, haematology, urinalysis, vital signs, physical examination, ECG and pulmonary function tests superseded by high resolution CT scans.
Secondary	**Secondary**
To compare the PK of cediranib when given alone for 7 days and in combination with AZD0530 for 21 days as measured by $C_{ss,max}$, $C_{ss,min}$, t_{max} and AUC_{ss} on Days 8 and 29.[a,b]	$C_{ss,max}$, $C_{ss,min}$, t_{max} and AUC_{ss} of cediranib on Day 8 (cediranib alone) and Day 29 (cediranib + AZD0530)
To determine the steady-state PK of AZD0530 when given in combination with cediranib for 21 days as measured by $C_{ss,max}$, $C_{ss,min}$, t_{max} and AUC_{ss} on Day 29.[b]	$C_{ss,max}$, $C_{ss,min}$, t_{max} and AUC_{ss} of AZD0530 on Day 29
To explore the efficacy of cediranib and AZD0530 given in combination as measured by RECIST, change in tumour size or changes in serological markers, such as CEA, HCG, AFP, CA125, CA153.[c]	Objective tumour response (RECIST) and change in tumour size. Change from baseline in serological markers (CEA, HCG, AFP, CA125, CA153) according to tumour type. Assessments were made at baseline, Week 7, Week 12 and every 8 weeks thereafter until disease progression.

[a] During the study, it was determined that the Day 8 PK profile samples were taken after dosing with AZD0530, and as such the Day 8 profile was not of steady-state cediranib alone. As a result, this secondary objective, as intended, could not be met.

[b] It should be noted that patients received AZD0530 in combination with cediranib for 22 days during the study.

[c] Insufficient data were available for the serological markers to draw meaningful conclusions.

Note: There were 2 exploratory objectives in the study (a PK objective to investigate further any large effect of cediranib on the steady-state PK parameters of AZD0530 and retrospective exploratory pharmacogenetic analyses), neither of which are reported in the main study report.

AEs: Adverse events; AFP: Alpha feto-protein; AUC_{ss}: Area under the plasma concentration-time curve during the dosing interval at steady-state; CA125: Cancer antigen 125; CA153: Cancer antigen 153; CEA: Carcinoembryonic antigen; $C_{ss,max}$: Maximum steady-state plasma concentration; $C_{ss,min}$: Minimum steady-state plasma concentration; CT: Computed tomography; ECG: Electrocardiogram; HCG: Human chorionic gonadotrophin; PK: Pharmacokinetic(s); RECIST: Response evaluation criteria in solid tumours; t_{max}: Time to maximum plasma concentration.

Study design

This was an open-label, multi-centre study to assess the safety and tolerability of ascending daily doses of cediranib in combination with daily doses of AZD0530, in patients with advanced solid tumours, with the exclusion of patients with prostate cancer. The purpose of this study was to assess the safety and tolerability of a regimen combining a potent vascular endothelial growth factor receptor inhibitor (cediranib) and a highly selective, specific Src kinase inhibitor (AZD0530) as a treatment for patients with advanced solid tumours. The first part of the study was a dose escalation phase investigating increasing doses of cediranib (20, 30 and 45 mg daily) in combination with AZD0530 (125 or 175 mg daily). Once the maximum tolerated dose was defined (decided by a safety review committee), a cohort expansion occurred in order to provide further safety data of the combination, assess the steady-state pharmacokinetics (PK) of cediranib and AZD0530, and provide preliminary efficacy data on cediranib in combination with AZD0530. The size of the cohort was based on the desire to collect adequate safety data at the tolerated combination dose, as well as the ability to detect large drug interaction effects on cediranib PK parameters.

Target patient population and sample size

Male and non-pregnant female patients, aged 18 years or older, with a histologically or cytologically confirmed cancer diagnosis and stage for whom no standard therapy existed; ≥1 measurable lesion by spiral computed tomography or conventional techniques as defined by response evaluation criteria in sold tumours; life expectancy of ≥12 weeks; World Health Organisation performance status of 0 to 2; and resting systolic blood pressure <150 mmHg and/or diastolic blood pressure <100 mmHg.

Six patients were to be recruited to each cohort to ensure a minimum of 3 patients were evaluable for assessment by the safety review committee. Up to 20 additional patients were to be recruited to the expanded cohort. The size of this cohort was based on the desire to collect adequate safety data at the tolerated combination dose as well as the ability to detect large drug interaction effect on cediranib PK parameters. However, due to limited PK samples, no formal statistical analyses were performed.

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

Cediranib (AZD2171) (20, 30 or 45 mg) and AZD0530 (125 or 175 mg) were both administered orally, once-daily in the morning, and at least 1 hour prior to the consumption of a meal or more than 2 hours after a meal had been ingested. Twelve batches of cediranib and 5 batches of AZD0530 were used during the study; individual batch numbers are provided in the main study report. Both cediranib and AZD0530 were manufactured by AstraZeneca.

Duration of treatment

Patients were to receive cediranib (20, 30 or 45 mg) alone for 7 days, followed by cediranib (20, 30 or 45 mg) combined with AZD0530 (125 or 175 mg) for 22 days, giving a total study treatment period of 29 days.

Patients could continue daily oral dosing with the combination of cediranib and AZD0530 indefinitely, assuming that they did not meet any criteria for discontinuation, were free from intolerable toxicity and, in the investigator's opinion, were receiving some benefit from the therapy.

Statistical methods

The primary analysis occurred when all patients had received 12 weeks of treatment, or had discontinued from the study prior to 12 weeks. All data collected to this point, which included data beyond 12 weeks for some patients in earlier cohorts, was used for the analyses.

During the study it was determined that the Day 8 PK profile samples were taken after dosing with AZD0530 (a single dose of AZD0530 was received prior to sampling) and, as such, the Day 8 profile was not of steady-state cediranib alone in individual patients. As a result, it was not possible to meet the secondary PK objective as intended. The formal statistical analysis was removed from the study at the time of developing the statistical analysis plan (prior to database lock).

The steady-state PK of cediranib was determined on Day 8 (in the presence of single dose AZD0530) and on Day 29 (in the presence of steady-state AZD0530). Geometric means (Gmeans) and 90% confidence intervals (CIs) were constructed for maximum steady-state plasma concentration ($C_{ss,max}$), minimum steady-state plasma concentration ($C_{ss,min}$) and area under the plasma concentration-time curve during the dosing interval at steady-state (AUC_{ss}) for both Day 8 and Day 29 by dose level. These data were compared with historical data from previous cediranib studies.

The steady-state PK parameters of AZD0530 in the presence of steady-state cediranib were determined on Day 29. Gmeans and 90% CIs for $C_{ss,max}$, $C_{ss,min}$ and AUC_{ss} were constructed and compared with historical data from previous AZD0530 studies.

Subject population

Forty-one patients were enrolled in this study and 39 patients received study treatment. The data cut-off date for the analysis presented for this study was 27 October 2008, which was the date on which the last patient either completed 12 weeks of treatment or had prematurely discontinued from the study. Eight patients were still ongoing in the study at the time of the data cut-off.

The first cohort of 6 patients received the starting dose of cediranib 20 mg and AZD0530 175 mg. No dose limiting toxicities (DLTs) were reported, therefore, this dose was deemed tolerable and dose escalation occurred.

A second cohort of 6 patients received cediranib 30 mg and AZD0530 175 mg; data from 5 evaluable patients in this cohort (1 patient was non-evaluable due to AZD0530 dose interruption) showed no DLTs and this dose was determined to be tolerable and dose escalation occurred.

A third dose group of 7 patients received cediranib 45 mg and AZD0530 175 mg; 1 patient was incorrectly enrolled (presence of unstable brain metastases not detected at screening) and so was replaced at this dose. One out of 6 evaluable patients experienced a DLT (Grade 3 hypertension related to cediranib). Although tolerated, this was the highest planned dose so further dose escalation did not occur, and an expansion cohort of 20 patients was enrolled at this dose.

In total, 31 of the 41 patients (75.6%) discontinued from the study; the most common reason for study discontinuation was worsening of the condition under investigation (22 patients [53.7%]). Discontinuation as the result of an adverse event (AE) or death was only reported in the cediranib 45 mg cohort (4 out of 27 patients [14.8%]).

The demographic and baseline characteristics were representative of the intended population. Although there was a significant spread in the site of the primary tumour, the most common primary tumour locations were colorectal (12/39 patients [30.8%], including the terms colon and rectal), pancreas (6/39 patients [15.4%]) or skin/soft tissue (4/39 patients [10.3%]). The patients were heavily pre-treated, as expected in a Phase I population of patients with advanced solid tumours.

Summary of efficacy results

Secondary objective

Some evidence of anti-tumour activity was observed in some patients following treatment with cediranib in combination with AZD0530 with over 30% of patients having a decrease in tumour size from baseline at some point in the study.

Summary of Pharmacokinetic results

Secondary objectives

At all doses of cediranib, there was good agreement in the cediranib PK parameters between Day 8 and Day 29 when comparing within patients, indicating no real change in the PK of cediranib following multiple versus single dose AZD0530 administration. On visual inspection of the individual patient data, the AUC_{ss}, $C_{ss,max}$ and $C_{ss,min}$ values were approximately dose proportional across the 20 to 45 mg dose range studied, suggesting no change in the PK parameters with cediranib dose.

In addition, based on comparison of the steady-state PK parameters of cediranib to historical steady-state data for cediranib at the same doses, there was no evidence to suggest that there was a clinically significant effect of AZD0530 (175 mg, single or multiple dose) on the steady-state PK of cediranib (20, 30 or 45 mg) when administered in combination, as the range of values obtained across the studies was similar.

Based on overall comparison of the AZD0530 data across all cohorts to historical steady-state data for AZD0530 at the same dose, there was no evidence to suggest a clinically significant effect of cediranib (20, 30 or 45 mg) on the steady-state PK of AZD0530 (175 mg) when administered in combination, as the range of values obtained across the studies was similar.

Summary of safety results

Primary objective

All 3 doses of cediranib were tolerated according to the protocol definition; however, the 20 and 30 mg doses were more sustainable than the 45 mg dose. The overall mean daily dose of cediranib was 19.5, 29.5 and 39.5 for the cediranib 20, 30 and 45 mg cohorts, respectively. The overall mean daily dose of AZD0530 was lower in patients receiving cediranib 45 mg (154.6 mg), compared with patients receiving cediranib 20 or 30 mg (166.3 and 163.4 mg, respectively). Reductions and pauses in cediranib treatment were more frequent for patients receiving cediranib 45 mg, compared with patients receiving the cediranib 20 and 30 mg doses; the majority of dose reductions and pauses in the cediranib 45 mg cohort occurred within the first 55 days of treatment.

All patients had at least 1 AE during the study. Overall, the most commonly reported AEs were hypertension (26/39 patients [66.7%]) and diarrhoea (24/39 patients [61.5%]). In addition, dysphonia was reported by 4/6 patients (66.7%) in the cediranib 20 mg cohort, and dysphonia, fatigue and thrombocytopenia were each reported by 3/6 patients (50.0%) in the cediranib 30 mg cohort. No clear dose relationship was seen for any of the AEs reported.

A higher percentage of patients had an AE of common terminology criteria adverse event (CTCAE) Grade 3 or higher in the cediranib 45 mg cohort (81.5%) compared with the cediranib 20 and 30 mg cohorts (33.3% in both cohorts). The most commonly reported AEs of CTCAE Grade 3 or higher were diarrhoea (5 patients [18.5%] in the cediranib 45 mg cohort) and fatigue (1 patient [16.7%] in the cediranib 20 mg cohort and 4 patients [14.8%] in the cediranib 45 mg cohort).

Adverse events leading to death were only recorded in the cediranib 45 mg cohort, but it should be noted that this cohort recruited 27 patients compared with only 6 patients in each of the other 2 cohorts. In total, 6 patients died during the course of the study, all of whom were in the cediranib 45 mg cohort: 3 patients died as a result of disease progression alone; 1 patient died as a result of disease progression and had a fatal AE (cerebellar haemorrhage); and 2 patients had fatal AEs (abdominal sepsis and pneumonia). The investigator considered there to be a reasonable possibility that the fatal AE of cerebellar haemorrhage was related to treatment with cediranib; neither of the other fatal AEs was considered to be treatment related.

Twenty-one patients (53.8%) had at least 1 serious adverse event (SAE) with an outcome other than death; a similar percentage of patients in each of the 3 cohorts had at least 1 SAE during the study (3 patients [50.0%] in each of the cediranib 20 and 30 mg cohorts; 15 patients [55.6%] in the cediranib 45 mg cohort). No preferred term was reported as an SAE by more than 2 patients in the study; the only SAEs reported by 2 patients in total were hyperbilirubinaemia, hypertension, pneumonia and pyrexia.

All patients who had AEs leading to treatment discontinuation were in the cediranib 45 mg cohort. None of the AEs leading to discontinuation were reported by more than 1 patient. In total, 5 patients (12.8%) had AEs that led to permanent discontinuation of treatment with

cediranib and 3 patients (7.7%) had AEs that led to permanent discontinuation of treatment with AZD0530.

Thyroid stimulating hormone increases were observed; no haematological, liver function or renal laboratory changes were observed that were considered to be clinically meaningful. Both systolic and diastolic blood pressure appeared to be well controlled; for most patients the highest blood pressure recorded was in the 'normal' or 'mild' hypertension categories. No clinically relevant changes in pulmonary function or electrocardiogram parameters were reported.