AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Cediranib (AZD2171)
Study Code	D8480C00029
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A Phase I, Open Label, Non-Randomised Study to Assess the Effect of Rifampicin on the Pharmacokinetics of Multiple Oral Doses of Cediranib (AZD2171, RECENTIN™), in Patients with Advanced Solid Tumours

Study dates: First patient enrolled: 9 September 2008
Last patient enrolled: 22 June 2009
Data cut-off: 30 July 2009

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

This study was conducted at 4 sites: 2 centres in Canada and 2 centres in the UK.

Publications

None at the time of writing this report.

Objectives

The objectives and their related variables are summarised in Table S1.

Table S1 Study objectives and variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	PK	To assess effects of rifampicin on cediranib steady-state PK, in patients with advanced solid tumours.	AUC_{ss}, $C_{ss,max}$, $C_{ss,min}$ and t_{max} in the presence and absence of rifampicin.
Secondary	Safety	To assess the safety and tolerability of cediranib in the presence of rifampicin.	AEs/SAEs, clinical chemistry, haematology, urinalysis, vital signs including blood pressure and physical examination, ECG.
	PK	To confirm the plasma exposure to rifampicin was sufficiently high to achieve adequate induction of CYP3A4 by rifampicin.	Urinary 6β-hydroxycortisol/cortisol ratio during rifampicin dosing (assessment of transport proteins and UDPGT).
Exploratory	Pharmacogenetic	A retrospective exploratory analysis of the role of genetic polymorphisms that may influence the ADME of cediranib.	Assessment of transporters and other ADME genes.

ADME: Absorption, distribution, metabolism, excretion; AE: Adverse event; AUC_{ss}: Area under the curve at steady-state; $C_{ss,max}$: Maximum steady-state cediranib concentration in plasma; $C_{ss,min}$: Minimum (trough) steady-state cediranib concentration in plasma; CSP: Clinical study protocol; ECG: Electrocardiogram; SAE: Serious adverse event; UDPGT: Uridine 5'-diphosphate glucuronosyltranserase; t_{max}: The time at which C_{max} was reached.

Study design

This was a Phase I, open label study to assess the effect of rifampicin, a CYP3A4 and transporter inducer, on cediranib PK in patients with advanced solid malignancies.

Sixty-four patients were administered cediranib 45 mg both in the presence and absence of rifampicin. Patients initially received cediranib 45 mg for at least 7 consecutive days before

treatment with rifampicin, for 7 consecutive days, to ensure that steady state was achieved. To be evaluable for the primary statistical analysis patients must have received at least 7 consecutive days of dosing with cediranib 45 mg followed by 7 consecutive days of dosing with rifampicin 600 mg plus cediranib 45 mg.

Target patient population and sample size

Male and female patients aged ≥18 years with advanced solid tumours, who had a World Health Organisation (WHO) performance status of ≤2, with a weight of at least 50 kg and a life expectancy of ≥8 weeks.

In total, 64 patients were administered cediranib 45 mg, and 58 of these patients received at least 1 dose of rifampicin.

Investigational product and comparator(s)

Rifampicin 600 mg (as 2 x 300 mg tablets) was to be taken 5 minutes before the co-administration of cediranib, which was to be administered at least 1 hour before or 2 hours after consuming food.

If required for tolerability reasons, cediranib dose reductions were permitted. However, patients who required dose reductions prior to Day 14 were not evaluable for the primary statistical analysis. Dose re-escalation of cediranib was not permitted at any time.

In the event of toxicity, cediranib dosing was withheld for a maximum of 14 days.

Batch numbers are provided in the Clinical Study Report.

Duration of treatment

Treatment with cediranib continued for an indefinite period, until a criterion for discontinuation was met (ie, disease progression, toxicity, death, consent withdrawal or another discontinuation criterion).

Criteria for evaluation - pharmacokinetics (main variables)

The primary outcome variables were area under the concentration-time curve at steady state (AUC_{ss}) and maximum (peak) plasma drug concentration at steady state ($C_{ss,max}$) of cediranib in the presence and absence of rifampicin

The secondary outcome variables were minimum (trough) plasma drug concentration at steady state ($C_{ss,min}$) and time to reach peak or maximum plasma drug concentration following drug administration (t_{max}) of cediranib in the presence and absence of rifampicin.

The exploratory outcome variables were plasma concentrations of rifampicin during treatment and 6β-hydroxycortisol/cortisol urine ratios before and during treatment with rifampicin.

Criteria for evaluation - safety (main variables)

The safety variables were:

- Adverse events (AEs)/Serious adverse events (SAEs)
- Laboratory findings (clinical chemistry, haematology, urinalysis)
- Vital signs including blood pressure (BP) and physical examination
- Electrocardiogram (ECG)

Statistical methods

The statistical analyses of each of the primary variables AUC_{ss} and $C_{ss,max}$ consisted of paired t-tests for each PK parameter of cediranib in combination with rifampicin against cediranib alone. Previous experience showed that these data conformed to a log-normal distribution and they were therefore to be logarithmically transformed prior to analysis. Results were reported as 90% confidence intervals (CIs) about the geometric mean ratio of cediranib in combination with rifampicin to cediranib alone for each parameter separately. Values of the ratio less than 1 indicated reductions in exposure of cediranib due to concomitant administration with rifampicin.

P-values were not presented for these analyses as tests of significance were not appropriate because small, consistent systemic exposure differences could be statistically significant (ie, different from a ratio of 1) but the CIs could still fall within the equivalence boundaries.

Subject population

In total, 89 patients were enrolled (ie, provided informed consent) into this open label, non-randomised study. Sixty-four patients received cediranib 45 mg study treatment; 39 were male and 25 were female. Of these, 58 patients received at least 1 dose of rifampicin.

Thirteen patients who completed PK sampling at Day 7 did not complete further PK sampling at Day 14. This was a result of disease progression in 5 patients, 1 patient death, 1 patient voluntarily discontinued, 1 patient met exclusion criteria (>14 day dose break) and a further 5 patients for whom reasons were not provided.

A total of 39 patients had discontinued study treatment at data cut-off (30 July 2009).

Overall, the demographic baseline characteristics were representative of the intended population.

Summary of pharmacokinetic results

There were 44 patients with evaluable paired $C_{ss,max}$ data and 41 patients with evaluable paired AUC_{ss} data. Comparison of the Day 7 and Day 14 data within each individual indicated that

for the majority of patients the $C_{ss,max}$ and AUC_{ss} were lower when cediranib was administered in the presence of rifampicin, compared to when cediranib was administered alone.

The geometric mean (gmean) AUC_{ss} and $C_{ss,max}$ for cediranib 45 mg decreased by 39% (90% CI: 34% to 43%) and 23% (90% CI: 16% to 30%), respectively, in the presence of rifampicin 600 mg. The gmean ratios for AUC_{ss} and $C_{ss,max}$ were below 1 and the 90% CIs were not within the pre-specified equivalence boundaries. For both parameters the upper limit of the 90% CI was below 1, indicating a statistically significant effect in the presence of rifampicin.

For $AUC_{ss,max}$, 11 out of 41 evaluable patients showed an increase or small decrease (ie, =25%) in the presence of rifampicin. Twenty-one patients had decreased between 25% and 50%, and the remaining 9 patients had decreases of more than 50%. For $AUC_{ss,max}$, the lowest observed was 0.36 (64% decrease). However, the minimum AUC_{ss} observed was similar on both days (Day 7=220 ng.h/mL, Day 14=243 ng.h/mL).

For $C_{ss,max}$, more than half of the patients (27 out of 44 evaluable patients, 61%) showed an increase or small decrease (ie, =25%) in the presence of rifampicin. Twelve patients had decreases between 25% and 50%, and the remaining 5 patients had decreases of more than 50%. For $C_{ss,max}$, the lowest ratio observed was 0.31 (69% decrease). However, the minimum $C_{max,ss}$ observed was similar on both days (Day 7=13.1 ng/mL, Day 14=16.6 ng/mL).

Although decreases in AUC_{ss} and $C_{ss,max}$ for cediranib were statistically significant, the magnitude of change was relatively small given the previously observed variability in the exposure of cediranib (Study D8480C00001) and was therefore considered to be of limited clinical significance.

Exposure to rifampicin was sufficiently high to achieve induction of CYP3A4, based on assessment of urinary 6β-hydroxycortisol/cortisol ratio.

Summary of safety results

All patients reported at least 1 AE during the study. In total, 43 (67.2%) patients reported AEs of CTC Grade ≥3 and 21 (32.8%) patients experienced an SAE. Fourteen (21.9%) patients reported a premature discontinuation of treatment with investigational product due to an AE.

The most commonly reported AEs were diarrhoea (52 [81.3%] patients), decreased appetite (40 [62.5%] patients), dysphonia (36 [56.3%] patients) and fatigue (36 [56.3%] patients).

The most commonly reported SAEs were vomiting (9 [14.1%] patients), nausea (4 [6.3%] patients), abdominal pain (3 [4.7%] patients) and dehydration (3 [4.7%] patients).

In total, 8 patients died either during treatment or within 30 days of last dose of cediranib; all of these were a result of disease progression. Two additional patients died as a result of disease progression more than 30 days after the last dose of cediranib.

In summary, cediranib was generally well tolerated in this study. The trends in laboratory data were consistent with previous cediranib studies. No new or unexpected safety issues were observed, and the safety of cediranib was not affected by the co-administration of rifampicin on Days 8 to 14 of cediranib administration.