Clinical Study Report Synopsis

Drug Substance	Cediranib (AZD2171)
Study Code	D8480C00032
Edition Number	1
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A Phase I, Open Label Study of the Pharmacokinetics and Safety of cediranib (RECENTIN™, AZD2171) following Single and Multiple Oral Doses in Patients with Advanced Solid Tumours with Various Degrees of Hepatic Dysfunction

Study dates:

First subject enrolled: 24 January 2008
Last subject last visit: 15 July 2010
Date of early study termination: 20 July 2010 (data cut-off)

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)

It was planned to recruit patients from at least 3 study centres in Denmark and The Netherlands. The first patient was enrolled on 24 January 2008 and the last patient to be included in this analysis was enrolled on 23 February 2010.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1: Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
To assess the single dose pharmacokinetics of cediranib, in patients with cancer with various degrees of hepatic dysfunction (defined by bilirubin levels).	AUC, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2\lambda z}$ and CL/F.
Secondary	**Secondary**
To assess the safety and tolerability of cediranib after single and multiple doses in patients with cancer with various degrees of hepatic dysfunction (defined by bilirubin levels).	Adverse events, vital signs, electrocardiograms, clinical chemistry, haematology, urinalysis, physical examination, proportion of patients with temporary or permanent withdrawals and proportion of patients eligible for pharmacokinetic analyses.
To assess the multiple dose pharmacokinetics of cediranib, in patients with cancer with various degrees of hepatic dysfunction (defined by bilirubin levels).	AUC_{ss}, $C_{ss,max}$, t_{max}, $C_{ss,min}$, TCP and R_{ac}.
To assess the single and multiple dose pharmacokinetics of cediranib, in patients with cancer with various degrees of hepatic dysfunction (defined by Child-Pugh classification).	AUC, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2\lambda z}$ and CL/F for single dose and AUC_{ss}, $C_{ss,max}$, t_{max}, $C_{ss,min}$, TCP and R_{ac} for multiple dose.
To determine the dose recommendation of cediranib, in patients with cancer with moderate and severe hepatic dysfunction.	DLT and PK data from patients with normal-mild and moderate hepatic dysfunction.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUC: area under the plasma concentration-time curve from 0 to infinity; AUC_{ss}: area under the plasma concentration-time curve at steady state; AUC_{0-t}: area under the plasma concentration-time curve from 0 to time t; CL/F: Apparent total body clearance of drug from plasma; C_{max}: maximum plasma (peak) drug concentration after single dose administration; $C_{ss,max}$: maximum plasma (peak) drug concentration at steady state; $C_{ss,min}$: minimum plasma (peak) drug concentration at steady state; t_{max}: Time to reach peak or maximal concentration following drug administration; $t_{1/2\lambda z}$: Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve; TCP: temporal change parameter; R_{ac}: accumulation ratio.

Study design

This was a Phase I, open-label, parallel group, multicentre study with 3 arms (normal-mild, moderate and severe hepatic dysfunction) to evaluate the pharmacokinetics and safety of single and multiple oral doses of cediranib in patients with advanced solid tumours with various degrees of hepatic dysfunction as defined by bilirubin levels.

Target subject population and sample size

It was planned to recruit approximately 16 patients per group for the normal-mild and moderate groups, and approximately 6 to 8 patients in the severe group.

The patients in this study were to have histological or cytological confirmation of advanced solid tumour (with the exception of prostate cancer), which was refractory to standard therapies or for which no standard therapy existed. Patients were to have a World Health Organisation performance status (WHO PS) of 0-2 and a life expectancy of at least 8 weeks. The study was to include patients with normal-mild (bilirubin ≤1.5 upper limit of the reference range [ULRR]), moderate (1.5 ULRR < bilirubin ≤3 ULRR) and severe (3 ULRR < bilirubin ≤5 ULRR) hepatic dysfunction.

Bilirubin levels have been chosen to define hepatic dysfunction in this study. Bilirubin as a measure of hepatic function evaluates hepatobiliary excretion and is one of the key contributing factors to the Child-Pugh classification.

Transaminases were not used to define hepatic dysfunction in this study because they are released from damaged liver cells and measure liver necrosis or injury rather than function and can be elevated for reasons other than liver disease. AST is found in many other organs besides the liver, including the kidneys, the muscles, and the heart.

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

Cediranib (AZD2171) was provided in 3 dosage forms: 15 mg, 20 mg and 30 mg tablets. Batch numbers are provided in the CSR.

Patients with normal-mild or moderate hepatic dysfunction were to receive a single oral 45 mg dose of cediranib on Day 1, followed by pharmacokinetics assessments and a minimum 7 day washout period (Day 2 onwards). Patients were then to commence once daily dosing of cediranib 30 mg for 21 days, with multiple dose pharmacokinetics assessments on the 21st day of multiple dosing.

If a decision was taken to dose patients with severe hepatic dysfunction these patients were to receive cediranib ≤45 mg as a single dose followed by a minimum 7 day washout, then continuous once daily dosing of cediranib ≤30 mg for 21 days. The decision to dose patients with severe hepatic impairment was to be made following review of a pre-specified minimum level of data on normal-mild and moderate hepatic impairment patients (see Section 3.2.1.1 of the Clinical Study Protocol for detailed information).

The dose of cediranib could be reduced on up to two occasions for any individual patient, to a minimum dose of 15 mg cediranib.

Duration of treatment

Patients were to receive a single dose of cediranib on Day 1. Following a minimum 7 day washout period, patients were to receive once daily dosing of cediranib for 21 days. After the multiple dosing period, patients could continue with daily dosing of cediranib indefinitely, assuming that they did not withdraw informed consent or meet a withdrawal criterion, were free from intolerable toxicity and, in the investigator's opinion, were receiving some benefit from the therapy.

Statistical methods

For the primary classification method, the bilirubin level measured within 3 days prior to the first dose of cediranib was to be used.

It was planned to recruit approximately 16 patients per group for the normal-mild and moderate groups, and approximately 6 to 8 patients in the severe group. If 16 patients had eligible single dose pharmacokinetic parameters in the normal-mild and moderate groups and if no mean change was observed between the groups, the 2-sided 90% confidence interval for the ratio of the geometric means (AUC and C_{max}) for the moderate and normal-mild groups would be [0.66, 1.52]. Similarly, if a 30% increase in exposure was observed, the corresponding 2-sided 90% confidence interval for the ratio of moderate to normal-mild would be [0.85, 1.98]. If a 50% increase in exposure was observed, the corresponding 2-sided 90% confidence interval for the ratio of moderate to normal-mild would be [0.99, 2.28].

Log_e-transformed AUC and C_{max} of plasma cediranib were to be analysed separately, using analysis of variance (ANOVA) models with factors included for hepatic impairment status (normal-mild, moderate or severe as defined by bilirubin levels). The analysis was to calculate adjusted ratios of geometric means for each comparison (moderate : normal-mild and severe : normal-mild) and corresponding 2 sided 90% confidence intervals for the pharmacokinetic parameters of interest.

The above analysis was also to be repeated for the secondary multiple dose pharmacokinetic parameters AUC_{ss} and $C_{ss,max}$, fitting ANOVA models on the log-transformed parameters with hepatic impairment groups included as factors. The single and multiple dose analyses were also to be repeated but using Child-Pugh boundaries, which were defined using the Day 1 pre-dosing laboratory assessments and physical examination results, in order to classify the patients rather than bilirubin levels alone.

All patients were to be included in statistical analyses, summaries and data listings according to the hepatic dysfunction classification group as appropriate. For pharmacokinetic data summaries by hepatic dysfunction group and formal analyses of pharmacokinetic parameters, only data from evaluable patients were to be included. Evaluable patients were those with sufficient pharmacokinetic data available in the presence of cediranib with no violations or

deviations that would have a significant impact on the pharmacokinetic parameters. In addition, for the multiple dose pharmacokinetic sampling, patients were to have received the investigational product continuously at the same dose for 7 consecutive days prior to pharmacokinetic sampling.

Subject population

Eighteen patients with normal-mild hepatic dysfunction and 12 patients with moderate dysfunction were entered and received the single dose of cediranib. No patient with severe hepatic dysfunction (according to bilirubin levels) was entered into the study. Four patients in the moderate group did not begin the multiple dosing phase of the study (1 patient discontinued due to rapid disease progression, 1 patient discontinued due to the AE of cardiac failure, 1 discontinued due to a deterioration of their condition and hyperbilirubinaemia and the fourth patient discontinued due to liver dysfunction). All 18 patients in the normal-mild group began the multiple dose phase, 2 patients did not complete 21 days of dosing (1 patient died due to the SAE of sepsis and 1 patient discontinued due to disease progression).

The demographic and baseline characteristics indicate that the study population was representative of the Phase I population being studied.

The baseline Child-Pugh characteristics were consistent with the Phase I population being studied. There were some differences in patient categorisation of hepatic dysfunction depending on whether bilirubin levels of Child-Pugh characteristics were used. In the normal-mild group this has resulted in 1 patient being classified as “moderate” according to Child-Pugh; and in the moderate group this resulted in 6 patients being classified as mild and 1 patient being classified as severe according to Child-Pugh.

At the time of data cut-off for this CSR, 3 patients continued to receive treatment and have reduced data collection.

Summary of pharmacokinetic results

The single dose pharmacokinetic parameters for cediranib 45 mg and the multiple dose pharmacokinetic parameters for cediranib 30 mg are summarised in Table S2 and Table S3, respectively.

Table S2 Summary of single dose pharmacokinetic parameters for cediranib 45 mg (Pharmacokinetic analysis set for single dose)

Parameter Statistic	Bilirubin		Child-Pugh		
	Normal-mild	Moderate	Mild	Moderate	Severe
C_{max} (ng/mL)					
n	18	12	23	6	1
Gmean (CV, %)	118 (55.9)	113 (50.6)	115 (50.9)	138 (49.3)	NC
Median (min, max)	119 (43.5-275)	106 (47.0-276)	114 (43.5-275)	136 (68.0-276)	47.0
AUC (ng.h/mL)					
n	16	11	20	6	1
Gmean (CV, %)	2005 (56.6)	2238 (62.4)	1857 (49.1)	3427 (57.6)	NC
Median (min, max)	2096 (894-4422)	1970 (1187-5645)	1931 (894-4422)	4265 (1296-5645)	1248

AUC: Area under the plasma concentration-time curve; C_{max}: Maximum plasma concentration; CV: Coefficient of variation; Gmean: Geometric mean; h: Hour; Max: Maximum.

There were no meaningful differences in the exposure (C_{max} and AUC) between normal-mild and moderate patients based on bilirubin or Child-Pugh classifications. The range of exposure values obtained here are in agreement with the range of values observed in previous monotherapy studies following single dose administration at the same dose (D8480C00001 and D8480C00021).

Table S3 Summary of multiple dose pharmacokinetic parameters for cediranib 30 mg (Pharmacokinetic analysis set for multiple dose)

Parameter Statistic	Bilirubin		Child-Pugh		
	Normal-mild	Moderate	Normal-mild	Moderate	Severe
$C_{ss,max}$ (ng/mL)					
n	16	8	20	3	1
Gmean (CV, %)	96.0 (43.4)	64.2 (59.1)	88.9 (49.9)	72.0 (65.3)	NC
Median (min, max)	98.3 (33.9-210)	53.7 (40.8-161)	90.6 (33.9-210)	68.4 (40.8-134)	42.2
AUC_{ss} (ng.h/mL)					
n	12	8	16	3	1
Gmean (CV, %)	1213 (43.8)	877 (53.3)	1106 (49.6)	958.1 (67.8)	NC
Median (min, max)	1079 (569-2355)	763 (527-1993)	1051 (569-2355)	924.0 (527-1802)	805

AUC_{ss}: Area under the plasma concentration-time curve during the dosing interval at steady-state; C_{max}: maximum plasma concentration; CV: Coefficient of variation; Gmean: Geometric mean; h: Hour; Max: Maximum.

There were no meaningful differences in the exposure ($C_{ss,max}$ and AUC_{ss}) between mild and moderate/severe patients based on Child-Pugh or bilirubin classifications.

Summary of safety results

A total of 18/18 patients in the normal-mild group and 8/12 patients in the moderate group entered the multiple dosing phase of the study. Of the patients who entered the multiple dosing phase, the mean (standard deviation [SD]) actual duration of exposure to cediranib was 108.7 [134.35] days [median 69.0 days] and 140.4 [118.99] days [median 114.0 days] for the normal-mild and moderate groups respectively. In addition, for both the normal-mild and moderate groups, the actual total number of treatment days was similar to the intended number (1957 days versus 2040 days, and 1123 days versus 1174 days, for the normal-mild and moderate groups, respectively).

AE data was based on all patients – including those who only received a single dose in the moderate group. All patients reported at least 1 adverse event (AE) during the study. The most commonly reported AEs were fatigue (16 [88.9%] patients versus 7 [58.3%] patients for the normal-mild and moderate groups respectively), decreased appetite (14 [77.8%] patients versus 5 [41.7%] patients for the normal-mild and moderate groups respectively) and diarrhoea (13 [72.2%] patients versus 6 [50.0%] patients for the normal-mild and moderate groups respectively).

A total of 17 patients (94.4%) in the normal-mild group and 10 patients (83.3%) in the moderate group experienced an AE which was ≥CTCAE Grade 3 in severity. The most commonly reported AEs of CTCAE Grade ≥3 were hypertension (5 [27.8%] patients versus 3 [25.0%] patients for the normal-mild and moderate groups respectively) and fatigue (5 [27.8%] patients versus 2 [16.7%] patients for the normal-mild and moderate groups respectively).

In total, 10 patients (7 patients in the normal-mild group and 3 patients in the moderate group) died either during treatment or within 30 days of last dose of cediranib; all but 1 of these deaths (sepsis in a patient in the normal-mild group) were a result of disease progression. Ten patients in the normal to mild group and 6 patients in the moderate group experienced an SAE. Four SAEs were reported by >1 patient: abdominal pain was reported by 2 patients (11.1%) in the normal-mild group, ascites by 1 patient (5.6%) in the normal-mild group and 1 patient (8.3%) in the moderate group, hepatic function abnormal was reported by 2 patients (16.7%) in the moderate group and pyrexia by 1 patient (5.6%) in the normal-mild group and 1 patient (8.3%) in the moderate group.

Discontinuations due to AEs were reported in 5 patients (27.8%) patients in the normal-mild group and 4 patients (33.3%) in the moderate group. Hepatic function abnormal was reported by 2 patients (16.7%) in the moderate group, this was the only discontinuations due to an AE reported by >1 patient.

Dose limiting toxicities (DLTs) were observed in 7 patients in the normal-mild group and 2 patients in the moderate group. DLTs included fatigue (3 patients), nausea (1 patient),

sepsis (1 patient), palmar-plantar erythrodysaesthesia (1 patient [moderate group]) and bilirubin elevations >1.5x Baseline levels for >2 weeks (5 patients, including 1 in the moderate group). However for 1 patient in the moderate group, this was not considered a true DLT after assessing the profile of their bilirubin levels.

There were no clinically significant changes in ECG findings during treatment.

Increases were observed in mean systolic and diastolic blood pressures as early as 2 hours post-dose (mean SBP increases of 8.4 mmHg in the normal-mild and 8.0 mmHg in the moderate group and mean DBP increases of 6.8 mmHg in the normal-mild and 7.5 mmHg in the moderate group). Nine of the patients (50.0%) in the normal-mild group and 7 patients (58.3%) in the moderate group had an adverse event of hypertension. Five of these events in the normal-mild group and 3 events in the moderate group were CTCAE Grade 3; no Grade 4 events were reported.

There were no new laboratory findings in this study. Small increases in the mean were observed for hematocrit, haemoglobin and red blood cell counts. Increases in thyroid stimulating hormone were seen with no associated reductions in free T4 or T3.