Drug product:	RECENTIN™	**SYNOPSIS**	
Drug substance(s):	Cediranib (AZD2171)		
Edition No.:	1		
Study code:	D8480C00021		
Date:	8 October 2008		

A Two-part, Open-label, Multi-centre, Phase II Study in Patients with Advanced Solid Tumours, Consisting of a Randomised 2-period Crossover Protocol to Determine the Effect of Food upon the Pharmacokinetics of a Single Oral Dose of AZD2171 (Part A), Followed by a Randomised, Parallel-group Protocol to Assess the Safety, Tolerability and Efficacy of Multiple Doses of AZD2171 Administered as Either a Fixed Daily Dose of 45 mg or an Individualised Dose-escalation Plan (Part B)

Publications

Jayson G, Evans TRJ, Harris A, Mitchell C, Kelly C, Middleton M, Fielding A, Laud P, Robertson J, Puchalski TA. The effect of food on the single dose pharmacokinetics of cediranib. Am Soc Clin Oncol 2008 (May 31 – June 5, Chicago, IL); Abst 14533

Study dates		**Phase of development**
First patient enrolled	7 June 2006	Therapeutic exploratory (II)
Last patient enrolled	8 October 2007	Date of data cut-off: 30 January 2008*

*The date of data cut-off was defined as the date 16 weeks after the last patient entered Part B of the study or had been withdrawn from the study prior to 16 weeks. Five patients remained on study treatment at data cut-off.

Study design

This was a Phase II, randomised, open-label, multi-centre study to determine if cediranib can be administered irrespective of food timing and to assess the tolerability and efficacy of multiple doses of cediranib. Part A of the study was a crossover design with 2 periods each lasting 10 days; patients were randomised in a 1:1 ratio to receive treatment with a single dose of cediranib 45 mg either fed then fasted or fasted then fed. In Part B of the study, patients were randomised in a 1:2 ratio to receive either a fixed-dose of 45 mg or to follow a dose-escalation approach (individualised dosing plan).

Target patient population

Male and female patients aged ≥18 years with histologically- or cytologically-confirmed advanced solid tumours, which were refractory to standard therapies or for which no standard therapy existed and who were expected to benefit from treatment with cediranib. Patients must have had a World Health Organisation (WHO) performance status between 0-2 and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.

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

Part A of the study: patients in **Sequence A** received single oral doses of cediranib 45 mg in tablet form in the fed then the fasted state. Patients in **Sequence B** received single oral doses of cediranib 45 mg in tablet form in the fasted then the fed state.

Part B of the study: patients in the **fixed-dose arm** were given cediranib 45 mg in oral tablet form once daily. The dose of cediranib 45 mg was administered as 2 tablets (30 mg + 15 mg) to be taken once daily. Patients in the **dose-escalation arm** were given a starting dose of cediranib 30 mg in oral tablet form once daily for 14 days. After at least 14 days, the option to increase the dose to 45 mg was allowed, if appropriate. Subsequent increases were permitted at least 14 days apart, in 15 mg steps, up to a maximum well-tolerated dose or 90 mg (personalised to the individual patient).

Duration of treatment

Part A of the study: each period was a minimum of 10 days in total (8 days of assessments with a minimum of 2 days without assessments in between the periods, to give a total of 10 drug-free days between doses).

Part B of the study: in the dose-escalation arm, each dose was administered for at least 14 days before dose-escalation occurred. Patients could continue daily dosing indefinitely in Part B of the study, assuming that they did not meet a withdrawal criterion, were free from intolerable toxicity and, in the investigator's opinion, were receiving some benefit from the therapy. All patients were to complete visits at Day 1 of Part B of the study (first day of treatment), weekly for the first 2 weeks and at intervals of 2 weeks thereafter (Days 15, 29 etc). After Week 16 (Day 112), those patients who reached their maximum well-tolerated dose or 90 mg for at least 2 weeks had visits every 4 weeks.

Objectives and associated variables

Objectives[a]	Variables
Primary objective: Part A The primary objective of Part A of the study was to compare the pharmacokinetic (PK) parameters of AZD2171 (cediranib) (area under plasma concentration-time curve from zero to infinity [AUC] and maximum plasma [peak] drug concentration after single dose administration [C_{max}]) obtained following single oral doses of 45 mg to patients in the fed and fasted state.	**Primary variables: Part A** Single dose AZD2171 PK parameters (AUC and C_{max}) in the fed and fasted state.
Primary objective: Part B The primary objective of Part B of the study was to compare the safety and tolerability of cediranib when given as either a fixed-dose or using a dose-escalation approach (individualised dosing plan).	**Primary variables: Part B** AEs. Vital signs (BP and heart rate). Electrocardiograms (ECG). Laboratory findings (clinical chemistry, haematology, urinalysis). Maximum well-tolerated dose for 6 weeks without treatment breaks or dose reductions. Total dose received over the initial 16 weeks.
Secondary objectives: Part A[b] To determine the PK parameters (area under the curve from time 0 to the last measurable time-point [$AUC_{(0-t)}$], time to reach peak or maximum concentration or maximum response following drug administration [t_{max}], terminal phase half-life [$t_{½\lambda z}$] and apparent total body clearance of drug from plasma [CL/F]) of cediranib in the fed and fasted state.	**Secondary variables: Part A[b]** Single dose AZD2171 PK parameters ($AUC_{(0-t)}$, t_{max}, $t_{½\lambda z}$, and CL/F).
To determine the effect of a single dose of cediranib on the QT interval corrected for heart rate (QTc).	QT, QTc according to Bazett's formula (QTcB) and Fridericia's formula (QTcF). Adverse Events (AEs). Vital signs (blood pressure [BP] and heart rate).
Secondary objectives: Part B[c] To compare the efficacy of cediranib monotherapy using either a fixed daily dose of 45 mg or an individualised dose-escalation plan.	**Secondary variables: Part B** Best overall RECIST response rates (ORR). Decrease in measurable tumour burden (sum of longest diameters) on RECIST. Progression-free survival (PFS).
To determine the effect of multiple doses of cediranib on the QTc interval.	QT, QTcB, QTcF

a Further exploratory objectives were undertaken and are presented in the full report together with the study results.

b The terminal elimination rate constant [λ_z] (see protocol) was not presented as the terminal phase half-life [$t_{½\lambda z}$] adequately describes the terminal phase disposition.

c An analysis of progression-free survival has been included in this study to give a better understanding of the RECIST data and of progression-free survival across the cediranib program. The decision to analyse for PFS was made prior to the date of finalising the Statistical Analysis Plan.

Statistical methods and sample size

Part A of the study: since little information was available to estimate the within-patient variation of AUC and C_{max} following a single dose of cediranib, a blinded estimation of variability was carried out when complete data were available from 12 patients. After this analysis, the final study numbers required to determine the effect of food on the PK parameters of a single dose of cediranib was calculated.

For the primary analysis to investigate the effect of food, an analysis of variance (ANOVA) model was used with factors fitted for the effect of sequence, patients within sequence, period and food (Fed/Fasted). For each of AUC and C_{max}, the effect of food was assessed using a confidence interval (CI) for the ratio of the parameter in the fed and fasted states. The final CI width was chosen in consideration of the interim analysis such that the overall Type I error of the study was no more than 5%. No effect of food on the plasma PK of AZD2171 was to be concluded if this interval lay entirely within the pre-specified equivalence boundaries (0.8 to 1.25) for both AUC and C_{max}.

For ECGs, the primary analysis presented the mean and 90% (95% one-sided) CI for the estimated effect of a single dose of cediranib on QTc (Fridericia's) at the time of individual C_{max}. The PK data from Part A were analysed on all randomised patients with at least one PK sample. The ECG data were analysed on an intent-to-treat basis to assess and the effect cediranib has on QTc prolongation. All other data were presented on an evaluable for safety basis; ie, all patients who received at least one dose of investigational treatment.

Part B of the study: the primary analysis of Part B of the study was performed when all patients in Part B of the study had received cediranib for 16 weeks or had been withdrawn from the study prior to 16 weeks.

Exposure was summarised for each randomised group by the median and quartiles and were compared between groups using a Mann-Whitney test. In addition, the maximum well tolerated dose, defined as the highest dose for which there is continuous dosing for a period of at least 6 weeks at that dose or higher, without dose breaks or interruptions, during the first 16 weeks of treatment, was summarised and compared across randomised group.

Patient population

Seventy-two patients from 4 centres in the United Kingdom were enrolled into the study (12 were not randomised). The first patient was enrolled on the 7 June 2006 and the date when the last patient completed 16 weeks of treatment (Part B) was 30 January 2008 (data cut off). Of the 60 patients who were randomised to the study, 54 (90%) received at least 1 dose of study treatment. Six randomised patients did not receive study treatment for the following reasons: voluntary discontinuation (2), condition under investigation worsened (1), suspicion of second malignancy (1), incorrect enrolment (1) and partial bowel obstruction (1). Five patients remained on study treatment at data cut-off.

The mean age of patients who were recruited into the study was 56 years (range: 19 to 74); 53.3% were male and 98.3% were Caucasian. The demographic characteristics in Parts A and B of the study were balanced ie, according to treatment sequence (Part A) and for the fixed-dose vs. dose-escalation phases (Part B). The majority of patients were WHO performance status 0 or 1, 27 (45.0%) and 28 (46.7 %), respectively. The most commonly reported location for primary tumour (excluding 'other') was ovary, colon and rectal with 9 (15.0%), 8 (13.3%) and 7 (11.7%) and for site of metastatic disease was respiratory, hepatic (including gall bladder) and lymph nodes with 30 (50.0%), 27 (45.0%) and 24 (40.0%) patients, respectively.

Primary variables: single dose AZD2171 PK parameters - fed and fasted state (Part A)

The primary objective of Part A of the study was to compare the pharmacokinetic (PK) parameters of AZD2171 (area under plasma concentration-time curve from zero to infinity [AUC] and maximum plasma [peak] drug concentration after single dose administration [C_{max}]) obtained following single oral doses of 45 mg to patients in the fed and fasted state.

A summary of AZD2171 45 mg single dose PK parameters, Gmean ratio and 94% CIs for ratio of fed to fasted, Part A is presented in Table S1. The level of confidence to be used in interval estimation for the food effect evaluation was 95% (overall alpha of 0.05). Following a planned interim analysis of the data, the width of the CI was required to be 94 rather than 95% in order to keep the overall alpha at 0.05.

Table S1 AZD2171 45 mg single dose PK parameters, Gmean ratio and 94% CIs for ratio of fed to fasted, Part A: PK analysis set

PK parameters	AZD2171 45 mg Fed State		AZD2171 45 mg Fasted State		Point estimate of Gmean ratio of fed to fasted	94% CI of Gmean ratio of fed to fasted
	n	Gmean	n	Gmean		
AUC (ng*h/mL)	30	1870.2	29	2454.2	0.762	0.663, 0.876
C_{max} (ng/mL)	31	87.3	30	130.0	0.672	0.567, 0.796

Food effect ratio = ratio of AZD2171 fed Gmean : AZD2171 fasted Gmean. Gmean : Geometric mean
CV : coefficient of variation

Both the AUC and C_{max} of AZD2171 were lower in the presence of food by a mean of 24 and 33%, respectively (94% CI: AUC, 12 to 34% lower and C_{max}, 20 to 43% lower). The CI for AUC crossed the lower equivalence boundary of 0.8 but the entirety of the CI was <1. The CI for C_{max} was entirely outside the equivalence boundary, indicating a clear food effect. The secondary PK analyses (Parts A) were consistent with the results for the primary analysis.

Primary variables during Part B (Safety)

The mean (SD) duration of exposure (days) during Part B of the study was lower in fixed-dose group (by 27 days) vs. dose-escalation group with 86.7 (90.2) vs. 113.7 (107.0) days, respectively. However, the mean (SD) average dose per day (mg) was similar with 33.79 (9.35) vs. 31.16 (9.03) mg, respectively.

During this study, the maximum well tolerated dose (MTD) was defined as the highest dose for which there is continuous dosing for a period of at least 6 weeks at that dose or higher, without dose breaks or interruptions, during the first 16 weeks of treatment. In the fixed-dose group, 2 patients achieved a MTD of 45 mg and 6: 30 mg (ie, having reduced from a starting dose of 45 mg). In the dose-escalated group, 2 patients achieved a MTD of 20 mg, 10: 30 mg, 5: 45 mg and 2: 60 mg. For the remaining patients in both groups, MTD was undefined.

All patients included in the safety population experienced at least 1 AE during the course of Part B of the study (Table S2).

Table S2 Number of patients who had at least 1 AE in any category during Part B: Safety analysis set

AE category	Number (%) of patients[a]		
	Fixed-dose	Dose-escalation	
	Cediranib 45 mg n=16	Cediranib 30 to 90 mg n=31	Total n=47
Any AE	16 (100.0)	31 (100.0)	47 (100.0)
Any causally[b] related AE	15 (93.8)	30 (96.8)	45 (95.7)
Any AE of CTCAE[c] grade 3 or higher	12 (75.0)	24 (77.4)	36 (76.6)
Any causally related AE of CTC grade 3 or higher	8 (50.0)	19 (61.3)	27 (57.4)
Any AE with outcome = death	1 (6.3)	2 (6.5)	3 (6.4)
Any causally related AE with outcome = death	0 (-)	2 (6.5)	2 (4.3)
Any SAE (including events outcome = death)	9 (56.3)	20 (64.5)	29 (61.7)
Any causally related SAE	5 (31.3)	12 (38.7)	17 (36.2)
Any AE leading to discontinuation of cediranib	4 (25.0)	4 (12.9)	8 (17.0)
Any causally related AE leading to discontinuation of cediranib	3 (18.8)	4 (12.9)	7 (14.9)
Any other significant AE (OAE)	0 (-)	0 (-)	0 (-)

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
b As assessed by the investigator.
c CTCAE Version 3.0.

The most commonly reported AEs reported during Part B in the fixed-dose group (cediranib 45 mg) were: *diarrhoea* (81.3%), *hypertension* (68.8%), *nausea* (68.8%), *vomiting* (62.5%) and *constipation* (62.5%) of patients. The most commonly reported AEs reported during Part B in the dose-escalated group (cediranib 30 to 90 mg) were: *diarrhoea* (80.6%), *hypertension* (74.2%), *nausea* (54.8%), *vomiting* (45.2%) and *constipation* (35.5%) of patients.

There were 3 (6.4%) patients with fatal AEs (*gastric perforation/gastrointestinal haemorrhage* [1]*, large intestine perforation* [1] *and abdominal pain* [1]) two of which were assessed by the investigator to be causally related to cediranib; the maximum dose prior to death was 45, 30 and 45 mg, respectively. The proportion of patients with SAEs in the fixed-dose vs. dose-escalated group was 56.3 vs. 64.5%, respectively and of these 31.3 vs. 38.7% respectively, was assessed by the investigator to be causally related to cediranib. The most commonly reported SAEs (*abdominal pain*, *diarrhoea* and *vomiting*) were reported at low incidences in both the fixed-dose vs. dose-escalated groups with 12.5, 6.3 and 0% vs. 9.7% patients (for each preferred term), respectively. In both groups, the remaining SAEs were reported at single incidences. Amongst the non-fatal SAEs, 2 patients experienced

GI perforations (an *intestinal perforation* and *gastrointestinal perforation*); the maximum dose prior to onset of the event was 45 mg in both cases. In addition to the gastrointestinal /intestinal perforations that were reported as SAEs, one patient died from an intestinal perforation that was considered to be disease progression by the investigator.

The proportion of patients experiencing AEs leading to discontinuation (DAE) of treatment was higher in the fixed-dose vs. dose-escalated group with 25.0 vs. 12.9%, respectively. All were reported at single incidences other than for *abdominal pain*, with 2 (6.5%) patients.

There were no clinically important time-dependent changes in haematology, clinical chemistry or urinalysis parameters following dosing with cediranib, and no apparent difference between the fixed-dose and dose-escalation groups. The results obtained were consistent with previous experience from other cediranib studies. There was no apparent effect of regimen (fixed-dose vs. dose-escalation) on blood pressure and no reports of CTCAE grade 3 or above hypertension or occurrences of hypertensive crisis; the maximum mean SBP and DBP were 140.2 and 86.6 mmHg respectively.

Secondary variables

Adverse events (Part A) - 35 (89.7%) patients in the safety population experienced at least 1 AE. The most commonly reported AEs were *hypertension*, *nausea*, *fatigue* and *lethargy* which were reported by 23.1, 23.1, 20.5 and 20.5% of patients, respectively. There were no fatal AEs and few SAEs or patients experiencing AEs leading to discontinuation of treatment.

ECG variables

Part A - the primary analysis was to determine the mean and two-sided 90% CI (corresponding to 95% one sided) for the estimated effect of a single dose of cediranib on QTcF at the time of individual C_{max}. The analysis compared baseline subtracted QTcF at the time of individual C_{max} (T_i-T_0) with baseline subtracted QTcF at the corresponding time in the control arm (C_i-C_0). The mean effect was –3.343 ms (90% CI: -9.13, 2.44; p=0.3329). The upper boundary of the CI is below 10 ms showing no clinically relevant effect of cediranib on cardiac repolarisation as determined by QTcF.

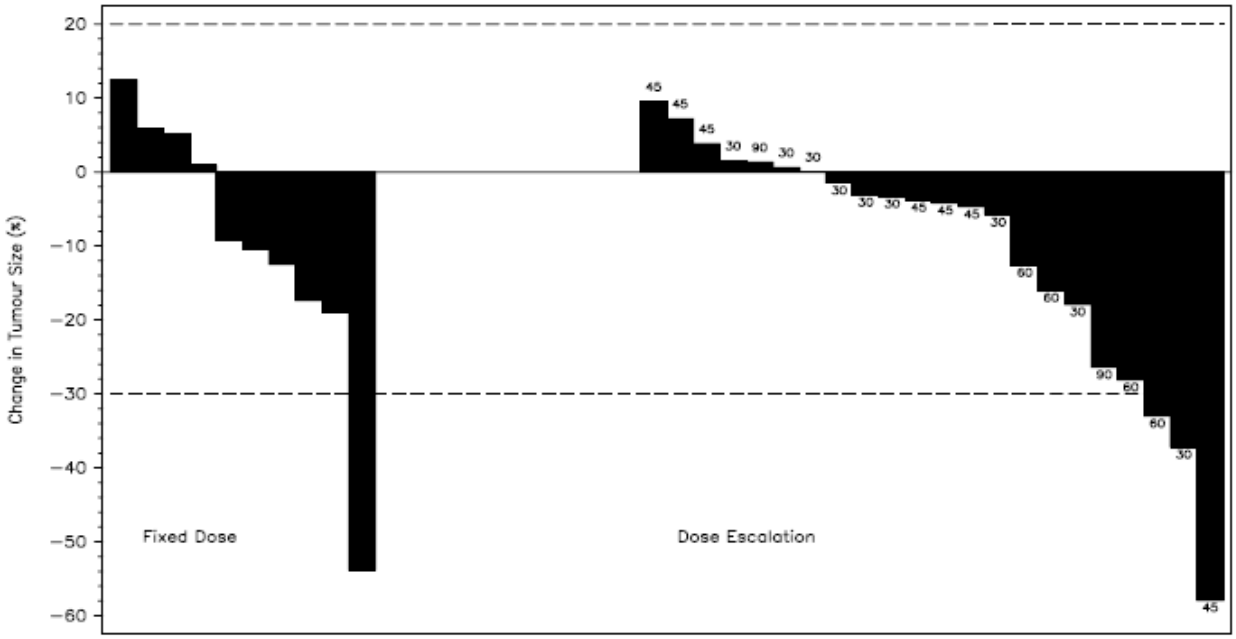
Part B - assessment of individual patient data during multiple daily dosing does not suggest that multiple daily dosing with cediranib causes any increase in QTcF over time.

A similar pattern of results was seen for QTcB.

Efficacy: ORR, changes in tumour size and PFS (Part B)

ORR - there were 1 (6.7%) and 3 (10.3%) patients who experienced an objective best response of partial response (PR) in the fixed-dose and dose-escalation groups, respectively.
Tumour size - in both the fixed-dose and dose-escalation groups, the proportion of patients showing a reduction as their best change was greater than the proportion of patients showing an increase in tumour size (Figure S1).

Figure S1 Waterfall plot for best reduction in tumour size for each patient during Part B: ITT analysis set



Dose escalation doses represent maximum dose attained during the study.
The change in tumor size presented is the best available for each patient.

Four patients in the fixed-dose group and 7 in the dose-escalation group had no post-baseline RECIST measurements and so are not included in Figure S1.

An analysis of PFS was performed, but due to the small number of events it is uninterpretable.