Drug Substance	AZD2171	**SYNOPSIS**	(For national authority use only)
Study Code	D8480C00023		
Edition Number	1		
Date	24 April 2008		

A Phase I, open-label, dose escalation study to assess the safety and tolerability of AZD2171 following single and multiple oral doses in patients in Japan with advanced solid malignancies

Study dates		**Phase of development**
First subject enrolled	19 October 2005	Clinical pharmacology (I)
Last subject enrolled	14 March 2007	

Objectives

The primary objective of this study was to determine the safety and tolerability of single and multiple oral doses of AZD2171 in patients with advanced solid malignancies.

The secondary objectives were:

- To evaluate the pharmacokinetics (PK) of single and multiple oral doses of AZD2171 in patients with advanced solid malignancies.
- To seek preliminary assessment of AZD2171 activity.

The exploratory objectives were:

- To seek preliminary assessment of AZD2171 activity.
- To determine the maximum tolerated dose (MTD) according to the reported dose limiting toxicity (DLT), if MTD existed in the range of the doses investigated in the ascending dose phase.

Study design

This study was separated into two phases:

Ascending dose phase:

The ascending dose phase was an open label, single, followed by multiple, ascending oral dose study.

Expanded cohort phase:

The expanded cohort phase was an open label, multiple dose study.

Target subject population and sample size

The ascending dose phase of the protocol was a single-centre study. A minimum of 3 patients with advanced solid malignancies were recruited at each dose level.

The expanded cohort phase of the protocol was a multi-centre study. Twelve patients with non-small cell lung cancer (NSCLC) and 12 patients with colorectal carcinoma (CRC) were recruited. PK samples were collected from the first 6 patients each in both NSCLC and CRC.

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

AZD2171 tablet 2.5 mg and AZD2171 tablet 10 mg were used in the study. The tablet(s) were administered orally with appropriate volume of water (approximately 150 mL) with the patient in an upright position. The patients took their medication on an empty stomach (i.e., no less than 1 hour prior to the consumption of a meal or more than 2 hours after a meal has been ingested). Patients were instructed to take their medication at approximately the same time each morning.

Ascending dose phase:

AZD2171 10, 20, 30 or 45 mg were given as single doses (Day 1). After 6 days (up to 8 days) washout period, the same dose as received in Day 1 was given, once daily, as multiple daily doses. Dose escalation was to continue until 45 mg or MTD was declared.

Expanded cohort phase:

The selected dose according to the result of the ascending dose phase was given once daily, as multiple doses.

Duration of treatment

Ascending dose phase: Single dose, then washout period for 6 days, and subsequently repeated dose. Patients received AZD2171 once daily until the criteria for discontinuation were met.

Expanded cohort phase: Patients received AZD2171 once daily until the criteria for discontinuation were met.

Variables

- **Safety**

  Adverse events

  Clinical laboratory tests

  Vital signs (blood pressure, pulse rate, body temperature)

  ECG

- **Pharmacokinetic**

  Single dose PK parameters (ascending dose phase):

  – C_{max}, t_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24h)}$, $t_{½\lambda z}$, MRT, CL/F, and V_{ss}/F

  Multiple dose PK parameters (both the ascending dose phase and the expanded cohort phase):

  – $C_{ss,max}$, $C_{ss,min}$, t_{max}, AUC_{ss}, R_{ac} and TCP (R_{ac} and TCP were only calculated in the ascending dose phase)

- **Pharmacodynamic**

  Tumour markers

  Biomarkers (Vascular endothelial growth factor [VEGF], soluble VEGF receptor-2 [sVEGFR2])

  Change in circulating endothelial cells (CEC) number and type

- **Efficacy**

  Change in tumour size (RECIST will be applied to patients with measurable disease)

Objective tumour response (according to RECIST criteria)

Statistical methods

The safety data were summarised using descriptive statistics.

Changes from baseline for continuous variables (clinical laboratory test, etc.) were also summarised.

C_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-24h)}$, $AUC_{(0-t)}$, AUC_{ss}, $C_{ss,max}$ and $C_{ss,min}$ were summarised using the geometric mean, CV (coefficient of variation), mean, standard deviation, minimum, maximum, and n.

- the geometric mean was calculated as exp [μ], where μ was the mean of the data on a log scale
- CV was calculated as 100 x √[exp (s^2)-1], where s was the standard deviation of the data on a log scale)

$t_{½\lambda z}$, CL/F, V_{ss}/F, MRT, TCP and R_{ac} were summarised using the arithmetic mean, standard deviation, minimum, maximum and n; and t_{max} using the median, minimum, maximum and n.

Subject population

- A total of 40 patients from two centres in Japan were registered into this study; 16 patients into the ascending dose phase and 24 patients into the expanded cohort phase.
- The median age of patients recruited into the ascending dose phase and the expanded cohort phase of the study was 55 years (range: 26 to 73 years); 60% were male and 100% were Oriental (Japanese) in race. The predominant tumour type was lung cancer (17 [42.5%] patients).
- Patients in the ascending dose phase had a variety of primary tumour types, which reflects the typical patient characteristics of phase I study for refractory solid tumour patient. Patients in the expanded cohort phase consisted of 12 patients with CRC and 12 patients with NSCLC as stated in the clinical study protocol.
- A total of 23 (57.5%) patients discontinued from the study treatment (11 [68.8%] patients in the ascending dose phase and 12 [50.0%] patients in the expanded cohort phase). Overall, the most common reason for discontinuation was disease progression (15 [37.5%]), while AEs accounted for 3 (7.5%) discontinuations. A total of 17 patients were ongoing in the study at the time of data cut-off date; 5 (31.3%) patients in the ascending dose phase and 12 (50.0%) patients in the expanded cohort phase. There were no protocol deviations leading to exclusion of patients from the PK, pharmacodynamic, efficacy, and safety analyses. No patients received concomitant medication that were prohibited by the protocol.

Summary of pharmacokinetic results

- Following a single dose, AZD2171 is orally available with the C_{max} ranging from 1.9 to 4.0 hours post dosing for each dose level. Concentrations declined in an apparent bi-exponential manner thereafter with a $t_{½\lambda z}$ ranging from 14.4 to 41.4 hours with arithmetic mean values ranging from 19.0 to 27.9 hours for each dose level.

- Steady-state plasma concentrations were predicted by the single dose PK, with TCP grand arithmetic mean values ranging from 0.99 to 1.31 for each dose level. This supports no time dependent changes in PK.

- Visual inspection of the trough plasma concentration values shows that steady-state plasma concentrations are attained after 7 days of repeated once daily dosing with AZD2171.

- Following multiple oral doses of 20 mg, the unbound $C_{ss,min}$ was 3.85 times above the HUVEC proliferation IC_{50}. This is supportive of the once-daily oral dosing of AZD2171.

Summary of pharmacodynamic results

- Biomarker assessments show an upward tendency in VEGF at 30 mg in the expanded cohort phase though the tendency in the ascending dose phase was unclear provably due to small number of patients. Decreases in sVEGFR2 were seen at Week 4 at all doses of AZD2171.

- There was no evidence of a dose relationship in both increases in VEGF and decreases in sVEGFR2.

Summary of pharmacokinetic-pharmacodynamic relationships

- No apparent relationship has been observed between elevations of SBP or DBP following multiple dosing and AUC_{ss} or $C_{ss,max}$.

- No apparent relationship has been observed between QTc prolongation or shortening and AUC_{ss} or $C_{ss,max}$. Isolated QTc increases were reported, of which no cases were judged clinically important by the investigators and none was reported as an AE.

- No apparent relationship has been observed between increases in VEGF or decreases in sVEGFR2 and AUC_{ss} or $C_{ss,max}$.

Summary of efficacy results

- RECIST data from the ascending dose phase and the expanded cohort phase of the study show:

- Out of 32 patients (10 in the ascending dose phase, and 22 [12 with CRC and 10 with NSCLC] in the expanded cohort phase) with baseline RECIST data, two confirmed partial responses (PR) were observed; one in a patient with alveolar soft tissue sarcoma in the ascending dose phase 45 mg and one in a patient with CRC in the expanded cohort phase 30 mg.

- Twenty-four patients experienced stable disease (SD); 3 patients in 10 mg, 1 patient in 20 mg, 1 patient in 30 mg, 3 patients in 45 mg in the ascending dose phase, 9 patients with CRC and 7 patients with NSCLC in the expanded cohort phase 30 mg.

- Waterfall plots showed that the majority of patients had some tumour reduction during the study.

- Two patients out of 10 evaluable patients in the ascending dose phase have continued with AZD2171 treatment for over a year with SD or PR as of data cut-off date.

Summary of safety results

- Dose escalations proceeded in accordance with the protocol, AZD2171 30 mg was established as the maximum tolerated dose (MTD) in the ascending dose phase of this study.

- Three patients in the ascending dose phase 45 mg experienced 4 DLTs (proteinuria and diarrhea; proteinuria; thrombocytopenia). These two cases of proteinuria at 45 mg did not have an accompanying nephrotic or nephritic syndrome.

- All 40 patients included in this study experienced one or more AEs that were considered by the investigator or AstraZeneca physician to be related to treatment.

- AZD2171 was generally well tolerated at oral daily doses of ≤30 mg; the most frequently (50% or over) reported AEs were: diarrhoea (14 [87.5%], 20 [83.3%]), hypertension (12 [75.0%], 20 [83.3%]), fatigue (12 [75.0%], 14 [58.3%]), palmar-plantar erythrodysesthesia syndrome (11 [68.8%], 16 [66.7%]), anorexia (11 [68.8%], 9 [37.5%]), and dysphonia (4 [25.0%], 13 [54.2%]) in the ascending dose phase and the expanded cohort phase, respectively. Most AEs were transient CTC grade 1 or 2 events.

- The most common (50% or over) laboratory test abnormalities considered as AEs were blood erythropoietin increased (15 [93.8%], 14 [58.3%]), blood TSH increased (12 [75.0%], 16 [66.7%]), proteinuria (11 [68.8%], 16 [66.7%]), AST increased (10 [62.5%], 5 [20.8%]), and ALT increased (9 [56.3%], 6 [25.0%]) in the ascending dose phase and the expanded cohort phase, respectively. Most cases were transient asymptomatic CTC grade 1 or 2.

- The majority of those AEs were considered to be related to AZD2171.

- The most common (10% or over) CTC grade 3 or 4 AEs were diarrhoea (3 [18.8%], 1 [4.2%]), neutropenia (2 [12.5%], 1 [4.2%]), and proteinuria (2 [12.5%], 2 [8.3%]) in the ascending dose phase and the expanded cohort phase, respectively. Most cases were considered to be related to AZD2171. One of these events (proteinuria, expanded cohort phase 30 mg) was judged as a CTC grade 4 event by the investigators because of involving nephrotic syndrome.

- A total of 9 (1 [6.3%], 8 [33.3%] patients in the ascending dose phase and the expanded cohort phase, respectively) had at least 1 SAE during the study. The most frequently (2 cases or more) reported SAE was proteinuria (3 [12.5%]) in the expanded cohort phase. No patients experienced a SAE at AZD2171 doses below 30 mg. There were no SAEs with fatal outcome during the study.

- Neither SAEs of hypertension nor severe hypertension as per blood pressure reading were observed. All AEs of hypertension were less than or equal to CTC grade 2.

- A total of 3 (1 [6.3%], 2 [8.3%] patients in the ascending dose phase and the expanded cohort phase, respectively) discontinued due to an AE in the study. The AEs leading to discontinuation were proteinuria (1 [6.3%], 1 [4.2%] in the ascending dose phase and the expanded cohort phase, respectively), hepatic function abnormal (1 [4.2%]), and nephrotic syndrome (1 [4.2%]) in the expanded cohort phase.