Drug Substance(s)	AZD2171	**SYNOPSIS**	(For national authority use only)
Study Code	D8480C00004		
Date	13 May 2008		

A Phase I, Open-Label Study to Assess the Safety, Tolerability and Pharmacokinetics of Ascending Multiple Oral Doses of AZD2171 when Co-administered with Fixed Multiple Oral Doses of ZD1839 (250 mg or 500 mg once daily) in Patients with Advanced Cancer

Study dates

First patient enrolled 5 May 2004

Last patient enrolled 22 February 2006

Phase of development

Clinical pharmacology (I)

Objectives and associated variables

The primary and secondary objectives and their associated outcome variables are summarised in Table S1.

Table S1 Study objectives and associated variables

Objective	Summary outcome variables
Primary	
To determine the safety and tolerability of multiple oral doses of AZD2171[a] when co- administered with fixed daily oral doses of ZD1839 (gefitinib, IRESSA™)[a] 250 mg or 500 mg to patients with advanced cancer	Adverse events, blood pressure, heart rate, respiration rate, electrocardiogram, clinical chemistry, haematology, urinalysis, and physical examination
Secondary	
To explore the pharmacokinetics (PK) of AZD2171 when given alone for 7 days and in combination with ZD1839 for 14 days (Parts A2 and B2)	$C_{ss,max}$, $C_{ss,min}$, t_{max}, AUC_{ss}
To make a preliminary assessment of the efficacy of AZD2171 and ZD1839 in combination as measured by objective response rate in patients with advanced cancer	Objective tumour response determined using Response Evaluation Criteria In Solid Tumours' (RECIST), duration of response
To explore the biological activity of AZD2171 when given in combination with ZD1839 by assessment of its effects on mean arterial pressure and biological markers	Blood pressure, biomarkers of angiogenesis and activated endothelial cells, skin biopsy granulation tissue assay (Part A2 and B2 only)

AUC_{ss}: Area under the plasma concentration-time curve during any dosing interval at steady-state; $C_{ss,max}$: Maximum steady-state drug concentration in plasma during dosing interval; $C_{ss,min}$: Minimum steady-state drug concentration in plasma during dosing interval; t_{max}: Time to reach peak or maximum concentration or maximum response following drug administration

[a] AZD2171 (ceditranib, RECENTIN™); RECENTIN and IRESSA are trademarks of the AstraZeneca group of companies.

Study design

This was an open, multi-centre study conducted in four parts (Parts A1, A2, B1 and B2). Parts A1 and B1 were dose escalation phases and Parts A2 and B2 were cohort expansion phases, as described below. In Parts A1 and B1, successive cohorts of 3 to 8 patients received daily oral doses of AZD2171 and either ZD1839 250 mg (Part A1) or ZD1839 500 mg (Part B1), in order to ensure at least 3 patients were evaluable in each cohort; the starting dose of AZD2171 in Part A1 was 20 mg and in Part B1 was 2 dose levels below the maximum tolerated dose (MTD) identified in Part A1. As outlined in the CSP, the intention was to determine the MTD of AZD2171 in combination with either ZD1839 250 mg or 500 mg, and then explore the pharmacokinetics (PK) of AZD2171 alone and in combination with ZD1839 in 2 expanded cohorts of 10 to 15 patients (Parts A2 and B2), in order to ensure at least 10 patients were evaluable in each cohort. In these cohorts, AZD2171 was to be taken as monotherapy once daily for 7 days and then co-administered with either ZD1839 250 mg (Part A2) or 500 mg (Part B2) for a further 14 days.

Target patient population and sample size

Approximately 80 male and female patients with advanced cancer.

Key inclusion criteria

Tumour progression on standard therapy or ineligible for standard therapy, life expectancy of 12 weeks or more, WHO performance status 0-2 (those with performance status 2 must have

been stable with no deterioration over the 2 weeks prior to study entry), and evidence of post menopausal status or negative urinary pregnancy test for female pre menopausal patients.

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

AZD2171 (0.5, 2.5, and 10 mg) and ZD1839 (250 mg) were manufactured and supplied by AstraZeneca as brown, film-coated tablets. The batch (ADM) numbers for AZD2171 were: 0.5 mg 10301F03; 2.5 mg 14101J03; 10 mg 30488K05, 32307D05, 14102G03, and 22298J04; the ADM numbers for ZD1839 250 mg were: 90540B02, 10782F03, 10828G03, 12328G03, and 13005J03.

Patients were instructed to take all study drugs orally and concurrently (ie, administered at the same time) with approximately 240 mL of water whilst in an upright position. The tablets were swallowed whole and not chewed, crushed or divided. Patients had to take their medication no less than 1 hour prior to the consumption of a meal or more than 2 hours after a meal had been ingested. Patients were instructed to take their medication at approximately the same time each morning.

In Part A1, the starting dose of AZD2171 was 20 mg, the maximum dose reached was 45 mg and the MTD for AZD2171 in combination with ZD1839 250 mg was identified as 30 mg. This dose was taken into the expanded cohort in Part A2. The protocolled starting dose of AZD2171 in Part B1 was 20mg, 2 dose levels below the MTD identified from Part A1. Because the 30mg dose was the MTD in Part A1, it was decided to take this dose forward into Part B2. However, because the 30mg dose was well tolerated in combination with ZD1839 500mg in Part B1, the protocol was amended to allow continued dose escalation in parallel to commencing Part B2. Two further doses were explored and the maximum dose reached in combination with ZD1839 500 mg was 45 mg.

Duration of treatment

In Parts A2 and B2, AZD2171 was taken as monotherapy once daily for 7 days and then co-administered with either ZD1839 250 mg (Part A2) or 500 mg (Part B2) for a further 14 days.

In all parts of the study, patients could continue daily oral dosing with AZD2171 and ZD1839 indefinitely, assuming they did not meet a withdrawal criterion, were free from intolerable toxicity, and, in the investigators opinion, were receiving some benefit from the therapy.

Statistical methods

Parts A1 and B1 primarily assessed safety and tolerability. There was no formal statistical analysis.

Pharmacokinetic data collected in Parts A2 and B2 were $\log_e$-transformed and analysed separately and combined using a paired t-test. Results were then back-transformed to provide a point estimate and the corresponding 2-sided 90% confidence interval (CI) for the ratio (AZD2171 + ZD1839/AZD2171). The intent of this analysis was to estimate the effect of

ZD1839 on the PK of AZD2171 in order to support the safety and tolerability conclusions, and not to formally demonstrate no clinically meaningful effect of ZD1839 on the PK of AZD2171.

Patient population

- A total of 106 patients were enrolled into this study; of these, 90 patients received study medication. Twelve patients were ongoing in the study at the time of database lock, all of whom were in Part B1.
- Of the 16 patient in Part A1, 3 patients, 5 patients and 8 patients were in the 20 mg, 30 mg and 45 mg dose groups, respectively. Of the 44 patients in Part B1, 8 patients were in the 20 mg, 25 mg and 30 mg dose groups, 13 patients were in the 37.5 mg dose group and 7 patients were in the 45 mg dose group.
- In total, 30 patients were recruited into Parts A2 and B2: 15 patients in each part.
- There were no protocol deviations leading to exclusion from the PK, pharmacodynamic, efficacy, and safety analyses.
- The median ages of patients who were recruited into Parts A and B of the study were 54.0 years (range: 31 to 78 years) and 55.0 years (range: 22 to 77 years), respectively; 74% and 71% were male, respectively. All patients in Parts A and B were Caucasian.
- The most common primary tumour types in Part A were colorectal (25.8%) and lung (12.9%); in Part B, the most common primary tumour types were renal (27.1%), lung (16.9%), colorectal (15.3%) and skin/soft tissue (15.3%).

Summary of safety results

- The maximum dose of AZD2171 reached in Part A1 was 45 mg; the MTD in combination with ZD1839 250 mg was 30 mg.
- The maximum dose of AZD2171 reached in Part B1, in combination with ZD1839 500 mg, was 45 mg[1].

[1] In Part B1, dose escalations proceeded in accordance with the original CSP up to the 30 mg dose level; dose escalation was then stopped, at the MTD identified in Part A1, and Part B2 of the study was initiated. A CSP amendment was subsequently made that enabled the dose in Part B1 to be escalated above the MTD declared in Part A1, allowing continued dose escalation in Part B1 after initiation of Part B2.

- The most frequently occurring DLT in Part A1 was hypertension (3 patients [18.8%]) and in Part B1 was diarrhoea (13 patients [29.5%]).

- The mean duration of treatment was 113.9 days (ranging from 2 to 395 days) in Part A and 144.7 days (ranging from 12 to 365 days) in Part B. Thirteen patients (41.9%) in Part A and 33 patients (55.9%) in Part B had a dose interruption and/or reduction during the study. Most dose interruptions and reductions occurred after the first 28 days and were most common in the 45 mg dose group.

- Five patients (16.1%) in Part A and 5 patients (8.5%) in Part B died during the course of the study; 3 of the deaths in Part A (2 events of euthanasia and 1 event of pulmonary haemorrhage) and 1 of the deaths in Part B (1 event of dyspnea) were the result of an AE. None of these deaths was considered by the investigator to be caused by AZD2171 or ZD1839, and all of the deaths were considered to be related to the patients' underlying disease.

Summary of adverse events in Part A of the study

- In total, 30 patients (96.8%) experienced at least 1 adverse event (AE) in Part A of the study; overall, 26 patients (83.9%) and 28 patients (90.3%) experienced an AE that was considered by the investigator to be related to AZD2171 or ZD1839, respectively. The most commonly reported AEs were diarrhoea (26 patients [83.9%]), anorexia (18 patients [58.1%]) and fatigue (17 patients [54.8%]). The most commonly reported AEs considered to be related to AZD2171 were diarrhoea (18 patients [58.1%]), hypertension (16 patients [51.6%]), anorexia (14 patients [45.2%]), and fatigue (14 patients [45.2%]).

- The only serious adverse events (SAEs) experienced by more than 1 patient in any dose group were dyspnoea (2 patients [13.3%] in Part A2) and euthanasia (2 patients [13.3%] in Part A2).

- A total of 7 patients (22.6%) discontinued due to an AE. The only AE leading to discontinuation experienced by more than 1 patient in any dose group in Part A was hypertension (2 patients [25.0%] in the 45 mg dose group of Part A1).

Summary of adverse events in Part B of the study

- All 59 patients in Part B of the study experienced at least 1 AE; overall, 58 patients (98.3%) had at least 1 event that was considered to be related to AZD2171 and all patients had at least 1 event that was considered to be related to ZD1839. The most commonly reported AEs were diarrhoea (58 patients [98.3%]), anorexia (45 patients [76.3%]) and fatigue (43 patients [72.9%]). The most commonly reported AEs considered to be related to AZD2171 were diarrhoea (50 patients [84.7%]), anorexia (43 patients [72.9%]), fatigue (41 patients [69.5%]), and hypertension (37 patients [62.7%]).

- The most frequently reported SAEs were diarrhoea (4 patients [6.8%]), dehydration (3 patients [5.1%]) and fatigue (3 patients [5.1%]).

- A total of 7 patients (11.9%) discontinued due to an AE. None of the AEs leading to discontinuation were experienced by more than 1 patient in any dose group.

Clinical laboratory evaluations

- Increases in haemoglobin and haematocrit were observed, with these increases being predominantly within the the normal ranges. Increases in thyroid stimulating hormone were observed, particularly at doses of 30 mg and above.

Summary of pharmacokinetic results

- In Part A2, a 21% reduction in AUC_{ss} was observed for AZD2171 30 mg when received in combination with ZD1839 250 mg for 14 days compared with AZD2171 30 mg when received alone for 7 days (ratio: 0.79; 90% CI: 0.62, 1.00). A smaller reduction in AUC_{ss} was observed in Part B2 (8%) for the same comparison: AZD2171 30 mg received in combination with ZD1839 500 mg compared with AZD2171 30 mg received alone (ratio: 0.92; 90% CI: 0.74, 1.15). Results of a pooled analysis of data from Parts A and B showed a statistically significant 16% reduction in AUC_{ss} (ratio: 0.84; 90% CI: 0.72, 0.98). In total, 19 patients (11 patients in Part A2 and 8 patients in Part B2) had calculable paired PK parameter data for AUC_{ss}

- In contrast with AUC_{ss}, the ratios for $C_{ss,max}$ were similar in Parts A2 and B2. In Part A2, a small reduction in $C_{ss,max}$ (4%) was observed for AZD2171 30 mg when received in combination with ZD1839 250 mg for 14 days compared with AZD2171 30 mg when received alone for 7 days (ratio: 0.96; 90% CI: 0.73, 1.26). In Part B2, a slight increase (1%) was observed for the same comparison of AZD2171 30 mg in combination with ZD1839 500 mg with AZD2171 30 mg alone (ratio: 1.01; 90% CI: 0.84, 1.21). Results of a pooled analysis of data from Parts A and B showed a 2% reduction in $C_{ss,max}$ (ratio: 0.98; 90% CI: 0.84, 1.15). A total of 23 patient (12 patients in Part A2 and 11 patients in Part B2) had calculable paired PK parameter data for $C_{ss,max}$.

Summary of efficacy results

- In Part A, 20 patients (64.5%) were evaluable for Response Evaluation Criteria In Solid Tumours (RECIST) response. In total, 1 patient (3.2%) had a partial response (1 patient who had a primary lung tumour) and 9 patients (29.0%) had a best response of stable disease.

- In Part B, 53 patients (89.8%) were evaluable for RECIST response. In total, 7 patients (11.9%) had a partial response (6 patients who had primary renal tumours and 1 patient who had a primary bone tumour) and 29 patients (49.2%) had a best response of stable disease.

- Overall, 18 patients (20.0%) had primary renal tumours, the majority of whom were in Part B of the study (16 patients). Of these 18 patients, 6 patients (33.3%) achieved a partial response and 7 patients (38.9%) had a best response of stable disease.

- For the 8 patients (8.9%) who showed a partial response to treatment during the study, the median (range) duration of response was 4.2 months (1.4 to 12.0 months).

Summary of pharmacodynamic results

- The majority of patients experienced an early, sustained increase (detectable at the first scheduled visit, on Day 7) in systolic blood pressure (SBP) and diastolic blood pressure (DBP) during Part A of the study; in Part B, the increase in SBP and DBP was less marked.

- Acute increases in VEGF, acute increases followed by stabilisation and reduction in basic fibroblast growth factor (bFGF), and acute decreases in soluble TIE-2 were observed; none of these changes was dose dependent. Reductions from baseline in soluble VEGFR (sVEGFR)-2 were observed, although no clear dose-relationship was identified.