Drug Substance(s)	AZD2171	**SYNOPSIS**	(For national authority use only)
Study Code	D8480C00003		
Date	4 July 2006		

A Phase I, Open-Label, Dose Escalation Study to Assess the Safety and Tolerability of AZD2171 Following Multiple Oral Doses in Patients With Advanced Prostate Adenocarcinoma

Publications

Four publications based on this study had been published at the time of preparing this clinical study report (CSR), and copies of these are provided in Appendix 12.1.11:

- Ryan C, Stadler WM, Roth BJ, Dong R, Puchalski TA, Koehler M, Small EJ. Safety and tolerability of AZD2171, a highly potent VEGFR inhibitor, in patients with advanced prostate adenocarcinoma. *2005* Prostate Symposium 2005: abstract 253.

- Ryan C, Stadler WM, Roth BJ, Puchalski TA, Morris C, Small EJ. Safety and tolerability of AZD2171, a highly potent VEGFR inhibitor, in patients with advanced prostate adenocarcinoma. Proc Am Soc Clin Oncol 2005; abstract 3049.

- Ryan C, Stadler WM, Roth R, Puchalski T, Morris C and Small EJ. Phase I evaluation of AZD2171, a highly potent VEGFR tyrosine kinase inhibitor, in patients with advanced prostate adenocarcinoma. Clin Cancer Res 2005;11: abstract A4.

- Ryan CJ, Stadler WM, Roth B, Puchalski T, Morris C and Small EJ. Phase I evaluation of AZD2171, a highly potent VEGFR tyrosine kinase inhibitor, in patients with hormone refractory prostate cancer (HRPC). 2006 Prostate Symposium 2006: abstract 261.

Study dates		**Phase of development**
First patient enrolled	16 March 2004	Clinical pharmacology (I)
Last patient enrolled	10 October 2005	

Objectives

The primary objective of this study was to establish the safety and tolerability of AZD2171 in patients with advanced prostate adenocarcinoma.

The secondary objectives of the study were:

- To explore the pharmacokinetic profile of AZD2171 when administered to patients with advanced prostate adenocarcinoma.
- To make a preliminary assessment of the efficacy of AZD2171 as measured by prostate-specific antigen (PSA) response in patients with advanced prostate adenocarcinoma.
- To make a preliminary assessment of the effect of AZD2171 on serum biomarkers of bone metastasis (bone alkaline phosphatase [b-ALP], serum procollagen type I N propeptide [PINP] and serum C-terminal telopeptide of type I collagen [CTx-I]), urine biomarker of bone metastasis (urine type I collagen-crossed-linked N telopeptide [NTx/Cr ratio]), plasma vascular endothelial growth factor (VEGF) and relevant surrogate biomarkers (eg, tumour microvessel density, Ki-67, markers of cell death within the tumour) in patients with advanced prostate adenocarcinoma.
- To make a preliminary assessment of the efficacy of AZD2171 as measured by objective response rate in patients with advanced prostate adenocarcinoma with measurable lesions.

Study design

This was a United States-based study that used a multicentre open-label, ascending multiple oral dose design to evaluate the safety and tolerability of AZD2171 in patients with advanced prostate adenocarcinoma.

The starting dose of AZD2171 was 1 mg and a total of 6 dose levels were evaluated. A minimum of 3 patients was to receive AZD2171 at each dose level. Approximately 40 patients were to be recruited in order to get 3 patients with a full data set per cohort. Patients continued daily oral dosing in 21-day treatment cycles, assuming they did not meet a

withdrawal criterion, were free from intolerable toxicity and, in the investigator's opinion, were receiving some clinical benefit from the therapy.

A maximum tolerated dose (MTD) and biological activity over a range of doses were determined and pharmacokinetic/pharmacodynamic (PK/PD) modelling was used to determine the appropriate dose(s) to be taken forward into future clinical studies.

Target patient population and sample size

Male patients with metastatic prostate cancer (with or without pain, and with or without progressive measurable disease) confirmed by bone scan within 3 months of study entry, or suspected based on documented biochemical progression after previous treatment with hormonal therapy.

As this was as an ascending-dose tolerance study, the number of patients was based on the desire to obtain adequate tolerability, safety, and pharmacokinetic data while exposing as few patients as possible to the study medication and procedures. A minimum of 3 patients received AZD2171 at each dose level (cohort). Approximately 40 patients were to be recruited, depending on the number of dose escalations/dose reductions/dose repeats.

Key inclusion criteria: men age 18 years and older; histological or cytological confirmation of prostate adenocarcinoma (symptomatic or asymptomatic); prior hormonal therapy, and/or no more than 1 prior chemotherapy regimen (including estramustine and/or corticosteroids) for the treatment of prostate adenocarcinoma; serum testosterone <50 ng/mL; World Health Organization, (WHO) performance status 0 or 1; and life expectancy of 12 weeks or longer.

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

AZD2171 was manufactured and supplied by AstraZeneca as brown, film-coated tablets. The batch numbers were as follows:

- 0.5 mg: 2000054450
- 2.5 mg: 2000054445 and 2000073198
- 10 mg: 200054447, 2000073027, and 2000078218.

The study drug was administered orally with approximately 240 mL of water. The tablets were swallowed whole and not chewed, crushed or divided. Patients were instructed to take their medication at approximately the same time each day, and at least 1-hour prior to the first meal of the day.

The starting dose of AZD2171 was 1 mg. The planned doses to be studied were:

Dose Level	Daily dose of AZD2171 (mg)	Dose Level	Daily dose of AZD2171 (mg)
1	1	8	15
2	1.5	9	20
3	2.5	10	25
4	3.5	11	30
5	5	12	37.5
6	7.5	13	45
7	10		

The starting dose was 1 mg. Doses were then escalated by 2 dose levels (eg, dose levels 3, 5, 7 etc) until 1 or more patients had experienced a DLT or 2 or more patients had a grade 2 toxicity. Thereafter, dose escalation was by single dose levels. No intra-patient dose escalation was undertaken in this study.

If the MTD had not been reached by Dose 13, additional doses could be administered following a safety committee review of the available safety, pharmacokinetic and pharmacodynamic data. In the absence of a DLT, increments of 33% of the previous dose level, rounded to the nearest 2.5 mg, could be made (eg, in this case, the dose level following dose level 13 would have been 60 mg). Once 1 or more patients had experienced a DLT, increments of 16% of the previous dose level, rounded to the nearest 2.5 mg could be made (eg, in this case, the dose level following dose level 13 would have been 52.5 mg).

Duration of treatment

Patients could continue daily oral dosing indefinitely assuming they did not meet a withdrawal criterion and, in the investigator's opinion, were receiving some clinical benefit from the therapy.

Variables

- **Pharmacokinetic**

  The following pharmacokinetic parameters were determined: $C_{ss,max}$, $C_{ss,min}$, t_{max}, AUC_{ss}, $AUC_{(0-24)}$, C_{max} and $R_{ac.}$

- **Pharmacodynamic**

  Change in the serum concentration of bone specific alkaline phosphatase (b-ALP), serum procollagen type I N propeptide (PINP), C-terminal telopeptide of type I collagen (CTx-I) and urine N telopeptide collagen cross-linked type I (NTx/Cr ratio),

change in plasma VEGF concentration, change in relevant surrogate biomarkers of tumour microvessel density, Ki-67 and markers of cell death within the tumour.

- **Efficacy**

  PSA response and objective tumour response by Response Evaluation Criteria In Solid Tumours (RECIST).

- **Safety**

  Adverse events (AEs), electrocardiogram (ECG), clinical chemistry, haematology, urinalysis (including urine protein/creatinine ratio α-1 microglobulin and N-acetyl-β-D-glucosaminidase), vital signs, and physical examination.

Statistical methods

No comparative statistical analysis was performed in this study; analysis was only descriptive and all data were summarised.

Patient population

- A total of 26 patients from 3 centres in the United States were enrolled into this study; the first patient was enrolled on 16 March 2004 and the last patient was enrolled on 10 October 2005. The study database lock date was 31 March 2006

- A total of 19 of the 26 (73.1%) patients were in the ≥65 year age range and none of the patients was below 50 years of age, ie, this was a predominantly elderly patient population that was considered to be representative of the broader population of prostate cancer patients. The majority of patients (92.3%) were Caucasian.

- The disease characteristics of the study population were representative of an elderly, advanced prostate cancer population and were consistent with the studies inclusion/exclusion criteria; all patients had a WHO performance status of 0 or 1, 16 of 26 (61.5%) patients had stage III or IV disease, and the majority of patients (80.8%) had Gleason scores in the range 7 to 10.

- All 26 patients entered into this study had received prior immunotherapy and/or hormonal therapy. Surgery and radiotherapy were also common prior treatment modalities, but only a minority of the patient population (10 of 26 [38.5%]) received prior chemotherapy. Although a wide variety of cancer therapies were administered to the patients prior to entering the study, Casodex (19 [73.1%]) and Lupron (18 [69.2%]) were the most commonly used.

- A wide variety of concomitant medications were taken throughout the study, including drugs that could affect hypertension, but none of these was considered to have interfered with the safety assessments performed during the study.

Summary of pharmacokinetic results

- Following a single dose AZD2171 is orally available with t_{max} ranging from 2.0 to 8.0 hours post dosing with an overall median value of 2.0 hours.

- Following oral multiple doses of AZD2171 ranging from 1 to 20 mg, the intersubject variability in $C_{ss,max}$ and AUC_{ss} expressed as the CV% ranged from 8.50 to 46.4%.

- Examination of the predose (trough) plasma support steady-state was achieved after 7 days of repeated once daily dosing.

- The arithmetic mean accumulation ratio for the 20 mg dose level of 2.15 is equal to an effective half-life of 26.6 hours.

- Following multiple oral doses of 20 mg, the unbound $C_{ss,min}$ is 4.44 times above the human umbilical vein endothelial cell (HUVEC) proliferation IC_{50}.

Summary of pharmacodynamic results

- No trends were observed for the markers of bone metastasis, ALP, PINP, CTx-I and urine NTx/Cr ratio.

- Increases in plasma VEGF from baseline were observed 8 hours after the first dose of study medication and on Day 21 of Cycle 1 in most patients receiving 5mg or higher doses of AZD2171.

Summary of pharmacokinetic/pharmacodynamic correlations

- No significant PK/PD relationships were observed between the change from baseline Cycle 1, Day 21 plasma VEGF and Cycle 1, Day 21 PSA with steady-state pharmacokinetic parameters of AUC_{ss}, $C_{ss,max}$ or $C_{ss,min}$.

- A significant relationship was observed between the change from baseline supine MAP and the steady-state pharmacokinetic parameter of $C_{ss,min}$ ($p = 0.05$, $R^2 = 0.48$). However, there was no significant relationship with AUC_{ss} or $C_{ss,max}$.

Summary of efficacy results

- No PSA responses (defined as a reduction in PSA from baseline of at least 50% that had to be confirmed by a second PSA value 4 or more weeks later) were observed during this study among the 19 patients who were evaluable for PSA response. However, examining PSA assessment data for individual patients shows there were 4 (15.4%) patients with reductions in PSA levels of >10%:

    - Patient E0002009 in the AZD2171 10 mg cohort had a 10.6% reduction from baseline at Cycle 1/Day 21.

  - Patient E0003005 in the AZD2171 20 mg cohort had consecutive PSA reductions across 4 cycles (Cycle 1, 27.2%; Cycle 2, 22.5%; Cycle 3, 35.1%; Cycle 4, 35.7%).

  - Patient E0001009 in the AZD2171 30 mg cohort had an isolated PSA reduction of 26.4% at Cycle 1/Day 8.

  - Patient E0001016 in the AZD2171 30 mg cohort had an isolated reduction of 35% from baseline at Cycle 1/Day 15.

- Overall, the data for percentage change from baseline in PSA show no consistent dose- or time-dependent changes; however these data are difficult to interpret because of the small numbers of patients at each dose level and time point.

- No objective responses were observed in the 14 patients with bi-dimensionally measurable disease. Four (28.6%) patients had a RECIST best response of SD and the majority of these (3 of 4 patients [75%]) were in the 20 mg cohort. One patient in the 20 mg cohort had a RECIST best response of PD.

Summary of safety results

- Overall, the 26 patients enrolled in this study were treated for a mean of 51.4 days, and for a maximum duration of 190 days. Four patients dose reduced; 2 patients in the 20 mg cohort and 2 in the 30 mg cohort.

- AZD2171 20 mg was established as the maximum tolerated dose (MTD) during this study. This decision was based on the observation that 3 patients within the 30 mg cohort experienced CTCAE grade 3 events of fatigue, muscle weakness, hypertension, and dehydration that were classified as DLTs.

- The majority of patients (23 of 26 [88.5%]) experienced 1 or more AEs during the course of this study; all patients at AZD2171 doses of ≥5 mg had at least 1 AE (Table S1). There were no deaths due to AEs in any dose cohort and no SAEs or discontinuations due to AEs at AZD2171 doses below 20 mg.

Table S1 Number of patients [a] (%) who had an adverse event in any category: all patients

Category [a]	AZD2171 dose (mg)						
	1 N=3	2.5 N=3	5 N=3	10 N=3	20 N=10	30 N=4	All doses N=26
Any adverse event	1 (33.3)	2 (66.7)	3 (100.0)	3 (100.0)	10 (100.0)	4 (100.0)	23 (88.5)
Drug-related [b] adverse events	0	1 (33.3)	2 (66.7)	1 (33.3)	9 (90.0)	4 (100.0)	17 (65.4)
Discontinuations due to adverse event	0	0	0	0	4 (40.0)	3 (75.0)	7 (26.9)
Discontinuations due to drug-related [b,] adverse event	0	0	0	0	4 (40.0)	3 (75.0)	7 (26.9)
Discontinuations due to serious adverse event	0	0	0	0	1 (10.0)	1 (25.0)	2 (7.7)
Discontinuations due to serious drug-related [b] adverse event	0	0	0	0	1 (10.0)	1 (25.0)	2 (7.7)
Any serious adverse event	0	0	0	0	2 (20.0)	1 (25.0)	3 (11.5)
Drug-related [b] serious adverse events	0	0	0	0	1 (10.0)	1 (25.0)	2 (7.7)
Any CTCAE [c] grade 3 or 4 adverse event	0	0	0	0	7 (70.0)	4 (10.0)	11 (42.3)
Drug-related [b] CTCAE [c] grade 3 or 4 adverse events	0	0	0	0	5 (50.0)	3 (75.0)	8 (30.8)

[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] Drug-related adverse events were those events that the investigator considered to be possibly related to study treatment.
[c] CTCAE grade NCI version 3.0.

- Overall, fatigue (13 [50%]), dysphonia (8 [30.8%]), headache (8 [30.8%]), hypertension (8 [30.8%]), diarrhoea (7 [26.9%]), and anorexia (7 [26.9%]) were the most commonly occurring AEs. In the AZD2171 20 mg cohort, hypertension (6 [60%]), headache (5 [50%]), dysphonia (5 [50%]), diarrhoea (4 [40%]), and fatigue (4 [40%]) were the most commonly occurring AEs. These events are consistent with the safety profile of AZD2171 reported previously for Study D8480C00001 and primarily represent CTCAE grade 1 (mild) or 2 (moderate) events.

- Dysphonia (8 [30.8%]), fatigue (8 [30.8%]), headache (8 [30.8%]), hypertension (8 [30.8%]), and diarrhoea (6 [23.1%]) were the most commonly reported AEs considered by the investigator to be causally related to treatment. Overall, there was no CTCAE grade 4 AEs considered by the investigator to be related to treatment.

- None of the 26 patients died during the study or the subsequent 30-day follow-up period.

- Five SAEs were reported by 3 (11.5%) patients across the 20 (single incidence of cancer pain and 2 incidences of transient ischaemic attack) and 30 mg (single incidences of fatigue and dehydration) cohorts. Four of these SAEs were considered by the investigator to be related to treatment and all of the events were CTCAE grade 3. Two of these drug-related SAEs were single occurrences of transient ischaemic attack in a patient with underlying diabetes and hypertension.

- A total of 7 (26.9%) patients discontinued AZD2171 due to an AE; all of these events were considered by the investigator to be related to treatment. A total of 12 AEs leading to discontinuation were reported by the 7 patients, and the majority of these events occurred as single frequencies.

- Hypertension and dysphonia were identified as other significant adverse events (OAEs) during this study. A total of 8 (30.8%) patients had an AE of hypertension during this study; all of these events were considered by the investigator to be related to study treatment, 4 of the 8 events were CTCAE grade 3, and 2 of the 8 events led to discontinuation. All of the AEs of hypertension were at AZD2171 doses of ≥20 mg. Eight (30.8%) patients experienced an AE of dysphonia; all of these events were considered by the investigator to be related to study treatment and were either CTCAE grade 1 (7 [87.5%]) or 2 (1 [12.5%]).

- There were no clinically relevant changes in the majority of the clinical laboratory parameters; increases in TSH and decreases in total thyroxine were observed along with increases in haemoglobin, haematocrit and erythrocytes, but the majority of these were within the normal range.

- Overall, there were no clinically relevant changes in the majority of the urinalysis parameters evaluated during this study. Increases in bilirubin were apparent in all AZD2171 dose cohorts, but these were not clinically significant. Increases in urine protein values were observed at AZD2171 doses of ≥20 mg; 1 (3.8%) patient in the 30 mg cohort developed CTCAE grade 2 proteinuria that was considered by the investigator to be related to AZD2171. One patient in the AZD2171 20 mg dose developed ++++ haematuria (urinary strip occult blood test) from baseline that was maintained until the end of the study, and 1 patient in the AZD2171 20 mg cohort developed ++++ haematuria that may have been a result of the underlining prostate cancer.

- There were no clinically relevant trends in vital signs or physical findings. Two patients in the AZD2171 20 mg cohort had QTc prolongation (defined as QTc ≥500 msec) with no clinically relevant findings.