Drug Substance(s)	AZD2171	**SYNOPSIS**	(For national authority use only)
Study Code	D8480C00001		
Date	5 December 2005		

A Phase I, Single-centre, 2-part, Open Study to Assess the Safety and Tolerability of AZD2171 following Single and Multiple Oral Doses in Patients with Advanced Solid Malignant Tumours

Publications

Three 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:

- Drevs J, Medinger M, Mross K, Zirrgiebel U, Strecker R, Unger C, Puchalski TA, Fernandes N, Robertson J, Siegert P. Phase I clinical evaluation of AZD2171, a highly potent VEGF receptor tyrosine kinase inhibitor, in patients with advanced tumors. Proc Am Soc Clin Oncol 2005;Abst 3002.

- Medinger M, Mross K, Zirrgiebel U, Strecker R, Koehler M, Clack G, Lewis J, Robertson J, Puchalski TA, Unger C and Drevs J. Phase I clinical evaluation of the

highly potent VEGF receptor tyrosine kinase inhibitor, AZD2171. Angiogenesis 2004;7:Supplement 1.

- Medinger M, Mross K, Zirrgiebel U, Strecker C, Wheeler G, Clack G, Lewis J, Puchalski TA, Unger C, and Drevs,J. Phase I dose-escalation study of the highly potent VEGF receptor kinase inhibitor, AZD2171, in patients with advanced cancers with liver metastases. Proc Am Soc Clin Oncol 2004;Abstract 3055.

Study dates		**Phase of development**
First patient enrolled	13 February 2003	Clinical pharmacology (I)
Last patient enrolled	26 January 2005	

Objectives

The primary objective of this study was to evaluate the safety and tolerability of ascending single and multiple oral doses of AZD2171.

The secondary objectives of the study were:

- To determine the pharmacokinetic (PK) profile following single and multiple oral doses of AZD2171.
- To assess the effects of AZD2171 on surrogate markers of activity to confirm biological activity over a range of doses by assessment of dynamic contrast enhanced magnetic resonance imaging (DCE MRI) [a], blood pressure (BP), tumour biopsy [b], wound angiogenesis [c], and biological markers.
- To make a preliminary assessment of antitumour activity by measurement of tumour response.

[a] DCE-MRI was performed, where possible, for all patients with liver metastases and at the investigator's discretion for patients without liver metastases.

[b] Tumour biopsy data were not available at the time of analysis of this study and are therefore not presented as part of this clinical study report (CSR). Any work done on these variables will be presented at a later date in a separate report.

[c] Wound angiogenesis was only assessed in patients with liver metastases.

Study design

This was a single-centre, ascending single, followed by multiple, ascending oral dose study assessing the safety and tolerability of AZD2171. The study was separated into two parts:

- **Part A**: Patients received a single dose of AZD2171 (Cycle 0) followed by an observation period for a minimum of 2 days. In Cycle 1, which commenced a minimum of 2 days after the single dose of AZD2171, patients started once daily administration with AZD2171, at the same dose administered in Cycle 0, for a period of 28 days.

- **Part B**: An open, randomised, parallel-group cohort expansion design phase. Approximately 36 patients (12 per dose group) with liver metastases were to be randomised to receive daily oral administration of AZD2171 at 1 of 3 doses. The doses were 3 well tolerated doses that had demonstrated preliminary evidence of biological activity in Part A of the study. In addition, up to 12 additional patients (up to 4 per dose group) with advanced solid tumours without liver metastases, were to be separately randomised to receive daily oral administration with AZD2171 at 1 of the 3 selected doses. This part of the study did not contain a Cycle 0.

Target patient population and sample size

Male and female patients with solid tumours with or without metastatic liver disease were recruited.

In Part A of the study, the primary aim was to perform an initial ascending-dose tolerance assessment, hence the number of patients was based on the desire to obtain adequate tolerability, safety, and PK 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 50 patients were planned to be recruited depending on the number of dose escalations/dose reductions/dose repeats for additional cohorts required.

In Part B, the primary aim was to assess the biological activity of AZD2171 over a range of 3 doses using surrogate markers. Approximately 36 patient with solid tumours and liver metastases were to be randomised to ensure 10 evaluable patients completed each dose level. In addition, up to 12 additional patients (up to 4 per dose group) with advanced solid tumours without liver metastases, were to be separately randomised. The sample sizes were based on both the feasibility of obtaining the required patients and the need to obtain adequate data for the assessment of biological activity of AZD2171.

Key inclusion criteria: histological or cytological confirmation of advanced solid tumour which is refractory to standard therapies or for which no standard therapy exists; for patients with metastatic liver disease, presence of a measurable liver lesion using magnetic resonance imaging (MRI); WHO performance status of 0, 1 or 2; life expectancy of at least 12 weeks.

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

AZD2171 was manufactured and supplied by AstraZeneca as brown, film-coated tablets in 0.5, 2.5, and 10 mg dosage strengths. The batch (ADM) numbers were as follows: 0.5 mg 92612K02, 2.5 mg 92613H02 and 14101J03, and 10 mg 10376G03 and 14102G03.

AZD2171 was administered orally with approximately 240 mL of water with the patient in the upright position. The tablets were swallowed whole and not chewed, crushed or divided. Patients took their medication on an empty stomach (ie, no less than 1 hour prior to the consumption of a meal or more than 2 hours after a meal had been ingested). In Part A of the study, the planned doses to be studied were:

Dose level	Dose of AZD2171 (mg)	Dose level	Dose of AZD2171 (mg)
Dose 1	0.5	Dose 8	10
Dose 2	1	Dose 9	15
Dose 3	1.5	Dose 10	20
Dose 4	2.5	Dose 11	25
Dose 5	3.5	Dose 12	30
Dose 6	5	Dose 13	37.5
Dose 7	7.5	Dose 14	45

The starting doses were AZD2171 0.5 and 1.0 mg. Doses were then escalated by 2 dose levels (ie, dose level 4, 6, 8 etc) until 1 or more patients had experienced a dose limiting toxicity (DLT). Thereafter, dose escalation was by single dose levels.

If the maximum well-tolerated dose had not been reached by Dose 14, additional doses were to be administered. Increments of up to 50% of the previous dose level could be made, provided <50% of patients in the cohort had experienced a DLT. In practice, only one additional dose level of 60 mg was administered during the conduct of the study.

The doses administered in Part B were 3 well tolerated doses of AZD2171 that had been shown to have preliminary biological activity in Part A of the study. Patients were dosed once daily in 28 day treatment cycles.

Duration of treatment

Part A

Cycle 0 was a single dose of AZD2171 followed by an observation period of a minimum of 2 days.

In Cycle 1 and every subsequent cycle, patients continued daily oral dosing indefinitely assuming they did not meet a withdrawal criterion, were free from intolerable toxicity and, in the investigator's opinion, were receiving some benefit from therapy.

Part B

Cycle 1 was 28 days in duration.

In Cycle 1 and every subsequent cycle, patients continued daily oral dosing indefinitely assuming they did not meet a withdrawal criterion, were free from intolerable toxicity and, in the investigator's opinion, were receiving some benefit from therapy.

Variables

- **Pharmacokinetic**

  Following single oral doses of AZD2171: C_{max}, t_{max}, half-life associated with the terminal slope of a semi-logarithmic concentration-time curve ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to infinity (AUC), apparent total body clearance of drug from plasma (CL/F), mean residence time (MRT), and apparent volume of distribution at steady-state (V_{ss}).

  Following daily dosing with AZD2171 for 28 days: maximum steady-state plasma concentration ($C_{ss, max}$), minimum steady-state plasma concentration ($C_{ss, min}$), t_{max}, AUC_{ss}, accumulation ratio (R_{ac}), and temporal change parameter (TCP).

- **Pharmacodynamic**

  Transfer constant used to quantify vascular permeability (k^{trans})and iAUC as determined by DCE-MRI; BP; wound angiogenesis (photographic visualisation of the wound and immunohistochemistry of granulation tissue); and biological markers (markers of angiogenesis and activated endothelial cells, the number and viability of circulating endothelial progenitor cells [CEPC], and the number of vascular endothelial growth factor receptor 1 [VEGFR-1] positive monocytes).

- **Efficacy**

  Tumour response.

- **Pharmacogenetics**

  Samples were collected for retrospective genotyping, but at the time of writing this CSR no analyses had been performed or were planned.

- **Safety**

  Adverse events (AEs), blood pressure, heart rate, respiration rate, electrocardiogram (ECG), clinical chemistry, haematology, urinalysis (including 24-hour collection for protein and creatinine), and physical examination.

Statistical methods

Due to the small number of patients included in each cohort in Part A, statistical analyses were not generally performed. As patients participating in Part B of the study were randomised to one of three doses, it was considered optimal to perform statistical analysis on data from this part of the study.

An assessment of objective tumour response in target lesions was made for patients participating in Parts A and B of the study. The number of patients falling in to the Response Evaluation Criteria In Solid Tumours (RECIST) categories of partial response (PR), stable disease (SD) and progressive disease (PD) were presented by dose level for patients from Parts A and B of the trial. In addition to the RECIST response categories outlined above, sub-categories of the RECIST best response category of SD have been reported as follows:

- unconfirmed PR: an isolated visit responses of PR that was not confirmed on the subsequent scheduled tumour assessment visit (for example, because the patient withdrew due to an AE between visits or because the subsequent visit showed stable disease), but with no other evidence of progressive disease.

- confirmed minor response (MR): response decreases from baseline of ≥10% and <30% observed on consecutive visits, with no other evidence of progressive disease.

Regression methods were used to assess the effect of dose on tumour size 56 days post first daily administration and to analyse the smallest target lesion size measured post dose, these data were also presented graphically.

Blood pressure data were summarised for each dose level. The change in SBP and DBP from pre- to post-dose at each time-point was calculated. Blood pressure data collected 28 and 56 days post first daily oral administration of AZD2171, for patients participating in Part B of the study, were analysed using regression methods to assess the dose response of the 3 doses of AZD2171. Absolute levels and mean changes from baseline from these analyses were presented with their corresponding 90% confidence intervals (CI).

Vascular permeability was assessed by measuring the percentage change in k^{trans} and iAUC60 using DCE MRI pre- to post-dose. These data were summarised for each dose level. Data from Part A of the study were used to make an assessment of the intra-patient variability in the vascular permeability parameters of k^{trans} and iAUC60.

It has been suggested that the threshold of activity for k^{trans} is a 40% reduction (pre- to post-dose). Intra-subject variability data from previous reproducibility studies indicated changes of greater than 40% were unlikely to be seen in the absence of therapy, this threshold was used to try and identify treatment-related reductions in DCE-MRI parameters. Data from scans conducted 2, 28 and 56 days post first administration of AZD2171, for patients from Part B, were analysed using regression methods to assess the dose response of the 3 doses of

AZD2171. Percentage changes from baseline were presented with corresponding 90% confidence intervals (CI).

An initial assessment of dose proportionality was made using PK data from Parts A and B of the study. Pharmacokinetic-pharmacodynamic (PK/PD) models were also fitted to explore the relationship between surrogate markers of activity (vascular permeability parameters and blood pressure) and PK parameters of AZD2171 plasma exposure.

For a further description of the statistical analysis conducted see the statistical analysis plan, Appendix 12.1.9.

Patient population

- A total of 83 patients were recruited into this study from a single centre in Freiburg, Germany. Of these, 36 (43.4%) and 47 (56.6%) patients were included in the multiple, ascending oral dose phase (Part A) and randomised parallel-group cohort expansion phase (Part B), respectively.

- The median age of patients who were recruited into Parts A and B of the study was 58 years (range: 19 to 78 years); 46% were male and 100% were Caucasian. The predominant tumour type was colorectal cancer (22 patients [27%]).

- The demographic characteristics of the patients were well balanced between the randomised dose groups in Part B of the study.

- A wide variety of concomitant medications were taken throughout the study by patients from both Parts A and B, but none of these was considered to have interfered with the safety assessments performed during the study. In the AZD2171 ≥20 mg dose groups, 29 (43%) patients were receiving treatment with concomitant medications that could affect hypertension at study entry compared with 44 (66%) patients after study entry.

- A total of 75 (90.4%) patients discontinued from the study treatment (35 [97.2%] patients from Part A and 40 [85.1%] patients from Part B). The majority of the discontinuations were due to disease progression, and 20 (24.1%) patients discontinued because of an AE. According to the study database, a total of 8 patients were ongoing in the study at the time of study database lock; 1 (2.8%) patient in Part A and 7 (14.9%) patients in Part B. There were no protocol deviations leading to exclusion of patients from the PK, pharmacodynamic, efficacy, and safety analyses.

Summary of pharmacokinetic results

- Following a single dose, AZD2171 is orally available with the C_{max} ranging from 1 to 8 hours post dosing. Concentrations declined in an apparent bi-exponential manner thereafter with a $t_{½\lambda z}$ ranging from 12.4 to 35.7 hours with an overall arithmetic mean value of 22.0 hours.

- Steady-state plasma concentrations were predicted by the single dose PK, with the grand arithmetic mean TCP value being 0.988. 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.

- Dose proportionate increase in $C_{ss,max}$ and AUC_{ss} were observed for AZD2171 doses ranging from 0.5 to 60 mg. However, further PK data are needed to make a definitive statement about linearity or dose proportionality.

- Following oral multiple doses of AZD2171 from 0.5 to 60 mg in Part A and B of the study, the intersubject variability in $C_{ss,max}$ and AUC_{ss}, expressed as the CV%, ranged from 20.7 to 87.6% in a dose dependent manner.

Summary of pharmacodynamic results

- DCE-MRI (iAUC60) data on Day 28 show dose-related decreases in iAUC60 over the range 0.5 to 60 mg (combined data from Parts A and B of the study). In the dose range explored in the randomised Part B (20, 30 and 45 mg), significant average reductions from baseline were seen for all 3 doses, and there was no evidence of a dose effect within this range.

- Blood pressure data show increases in mean SBP and DBP were apparent over time. These changes were most marked at AZD2171 doses of ≥20 mg.

- There were no consistent changes in either percentage CEPC or CEPC index in Parts A or B of the study.

- Data from the wound angiogenesis assay did not allow an evaluation of the biological activity of AZD2171; there were insufficient data available from the photographic evaluation following punch biopsy, and the normal skin biopsy is to be analysed after the finalisation of this CSR.

- Assessment of soluble markers of angiogenesis show increases in VEGF have been detected at all doses, and time- and dose- dependent reductions in soluble VEGFR-2 (sVEGFR-2) have been documented at doses up to and including 20 mg. Reductions in sVEGFR-2 were apparent at AZD2171 doses above 20 mg, but there was no evidence of a dose relationship within this range. No trends were observed for basic fibroblast growth factor (b-FGF), sE-selectin, sVEGFR-1, and interleukin 8 (IL-8), but there was a suggestion of a dose threshold above AZD2171 10 mg for sTIE2.

Summary of pharmacokinetic-pharmacodynamic relationships

- Pharmacokinetic parameters of AZD2171 plasma exposure following both single and multiple doses of AZD2171 ranging from 0.5 to 60 mg do not appear to be major determinants of observed SBP or DBP elevations (R^2 range 0.00-0.23). However, the relationships between DBP elevations and AUC_{ss} and $C_{ss,max}$ were significant ($p<0.05$).

- Pharmacokinetic parameters of AZD2171 plasma exposure following multiple doses ranging from 0.5 to 60 mg appear to be major determinants of the decrease in tumour vascular permeability as described by the DCE-MRI variables of iAUC60 (R^2 range 0.33-0.49). The relationship between the tumour vascular permeability parameters and multiple dose PK parameters derived for AZD2171 doses in the range 0.5 to 60 mg were significant ($p<0.05$). However, when the dose range was restricted to the doses explored in the randomised Part B (20, 30 and 45 mg) weaker relationships were observed.

Summary of efficacy results

Data from an objective response evaluation conducted according to RECIST criteria along with a formal analysis of tumour size in AZD2171-treated patients showed the following:

- RECIST data from Part A and B of the study show:

  – 2 confirmed partial responses (PR) were seen; one in a patient with prostate cancer in the 45 mg cohort and one in a patient with renal cancer in the 60 mg cohort

  – 22 stable diseases (SD), including 2 patients with a single decrease of at least 30% (unconfirmed PR) and 7 patients with consecutive decreases of between 10% and 30% (confirmed minor responses [MR]).

- There was evidence of a dose-related increase in the percentage of patients with SD or better, and reductions in patients with progressive disease.

- An analysis of size of the target metastatic liver lesion at Day 56 conducted in the randomised Part B of the study shows a trend towards increased tumour reduction with increasing dose of AZD2171. The changes in tumour size were similar for the 30 mg and 45 mg cohort, but there appeared to be much smaller changes in the 20 mg cohort. Indeed, examining the estimated maximum per cent reduction in target lesion size shows there is a trend towards a greater reduction with AZD2171 45 mg compared to AZD2171 20 mg (one-sided $p=0.03$). There was an overall significant difference in change in tumour size between the doses at the 10% significance level ($p=0.08$).

Summary of safety results

- Dose escalations proceeded in accordance with the protocol, and the maximum single dose reached in the dose escalation phase (Part A) of this study was 60 mg.

- AZD2171 45 mg was established as the maximum tolerated dose (MTD) during this study. This decision was based on the observation that although few DLTs occurred in the 60 mg cohort (see Section 8.3.3), the investigator reported that AZD2171 appeared to be less well tolerated by patients in this cohort, with an increased incidence of nausea and dysphonia compared to previous cohorts. Therefore, AZD2171 doses of 20, 30 and 45 mg were taken forward for further evaluation in the randomised, cohort expansion phase (Part B) of the study.

- All 83 patients included in this study experienced one or more AEs (see Table S1). A total of 61 (73.5%) patients experienced an AE that was considered by the investigator or AstraZeneca physician to be related to treatment.

- AZD2171 was generally well tolerated at oral daily doses of ≤45 mg: the most frequently reported AEs were fatigue (47 [56.6%]), diarrhoea (39 [47.0%]), nausea (34 [41.0%]), dysphonia (30 [36.1%]), hypertension (29 [34.9%]), vomiting (26 [31.3%]), and anorexia (24 [28.9%]). The incidences of fatigue and nausea were similar across all of the doses investigated, but there was some evidence of a dose response for dysphonia, diarrhoea and hypertension. Dysphonia and hypertension were not reported at AZD2171 doses below 20 mg.

- The most commonly reported drug-related AEs were dysphonia (30 [36.1%]), hypertension (25 [30.1%]), and diarrhoea (24 [28.9%]). For each of these drug-related AEs, there was evidence of a dose response.

- There were no drug-related CTC grade 3 or 4 AEs at AZD2171 doses of ≤10 mg. The most common drug-related CTC grade 3 or 4 AEs were hypertension (13 [15.7%]), hypertensive crisis (3 [3.6%]), gamma-glutamyl transferase.(GGT) increased (3 [3.6%], palmar-plantar erythrodysaesthesia syndrome (3 [3.6%]), and diarrhoea (2 [2.4%]). The majority of these events were of CTC grade 3. The remaining CTC grade 3 or 4 AEs occurred as single incidences.

- Twenty-one DLTs were reported during this study. Hypertension was the most frequently occurring DLT (7 [33.3%] incidences), followed by hypertensive crisis (2 [9.5%] incidences). The remainder of the DLTs occurred as single incidences.

- Three patients were reported to have died as a result of an adverse event. The AEs associated with the deaths were malignant ascites (AZD2171 1 mg), ileus (bowel stasis) (AZD2171 20 mg), and cerebral haemorrhage (AZD2171 60 mg). None of these deaths was considered by the investigator to be caused by AZD2171.

Table S1 Number of patients [a] (%) who had an adverse event in any category in study Parts A and B combined (safety population)

Category [a]	Dose (mg)									
	0.5 N=3	1 N=3	2.5 N=3	5 N=3	10 N=4	20 N=19	30 N=21	45 N=19	60 N=8	All doses N=83
Any adverse event	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	4 (100.0)	19 (100.0)	21 (100.0)	19 (100.0)	8 (100.0)	83 (100.0)
Drug-related [b] adverse events	2 (66.7)	0	1 (33.3)	0	1 (25.0)	15 (78.9)	19 (90.5)	16 (84.2)	7 (87.5)	61 (73.5)
Discontinuations due to adverse event	0	0	0	0	0	4 (21.1)	6 (28.6)	6 (31.6)	4 (50.0)	20 (24.1)
Discontinuations due to drug-related [b] adverse event	0	0	0	0	0	2 (10.5)	3 (10.0)	4 (21.1)	3 (37.5)	12 (14.5)
Discontinuations due to serious adverse event	0	0	0	0	0	3 (15.8)	5 (23.8)	4 (21.1)	2 (25.0)	14 (16.9)
Discontinuations due to serious drug-related [b] adverse event	0	0	0	0	0	2 (10.5)	2 (9.5)	3 (15.8)	1 (12.5)	8 (9.6)
Any serious adverse event	2 (66.7)	0	0	1 (33.3)	0	11 57.9)	10 (47.6)	11 (57.9)	6 (75.0)	41 (49.4)
Drug-related [b] serious adverse events	0	0	0	0	0	6 (31.6)	5 (23.8)	5 (26.3)	2 (25.0)	18 (21.7)
Any CTC [c] Grade 3 or 4 adverse event	2 (66.7)	0	0	1 (33.3)	0	11 (57.9)	11 (52.4)	13 (68.4)	8 (100.0)	46 (55.4)
Drug-related [b] CTC [c] Grade 3 or 4 adverse events	0	0	0	0	0	7 (36.8)	8 (38.1)	7 (36.8)	5 (62.5)	27 (32.5)
Deaths due to adverse event	0	1 (33.3)	0	0	0	1 (5.3)	0	0	1 (12.5)	3 (3.6)

[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] CTC Grade NCI version 2.0.
N Number of patients.

- A total of 41 patients (49.4%) had at least 1 SAE during the study. The most frequently reported SAEs were hypertension (9 [10.8%]), ileus (4 [4.8%]), and hypertensive crisis (3 [3.6%]). Each of these SAEs occurred at AZD2171 doses of 20 mg and higher.

- Eighteen patients (21.7%) experienced a total of 24 SAEs that were considered by the investigator to be related to study treatment. Hypertension and hypertensive crisis were the most commonly reported drug-related SAEs, accounting for 8 and 4 of the 23 events, respectively.

- A total of 20 (24.1%) patients discontinued due to an AE in the study; 12 (14.5%) patients discontinued due to drug-related AEs. The most commonly reported AEs leading to discontinuation were hypertension (4 [4.8%]), fatigue (3 [3.6%]), diarrhoea (2 [2.4%]), and blood bilirubin increased (2 [2.4%]).

- Dose-related increases in haemoglobin, haematocrit and erythrocytes were observed at AZD2171 doses of ≥20 mg. In only 2 cases were these changes considered to be clinically relevant. A number of patients had increases from baseline in erythropoietin to levels outside of the normal range (0-19mU/mL); however, because erythropoietin was measured at just one time point (post-dose, Day 28) in Part B only, the data were not suitable for analysing the putative relationship with haematocrit.

- Dose-related, mean-within patient increases from baseline in thyroid stimulating hormone (TSH) and decreases in total thyroxine were seen at AZD2171 doses of ≥20 mg. Free T3 and T4 levels remained unchanged. There were no associated clinical symptoms of hypothyroidism. There were no other clinically relevant changes in clinical laboratory parameters.

- Overall, there were no observed dose-related changes in creatinine or creatinine clearance, and no clinically relevant dose-related urinalysis trends for bilirubin, glucose, ketones, or blood. Proteinuria (defined as urine dipstick protein ++ or higher on 2 consecutive visits) was observed in 6 (12.5%) patients at doses of AZD2171 30 mg and above.

- With the exception of BP, there were no clinically relevant trends in vital signs, physical findings, or ECG observations.