Drug Substance(s)	AZD2171	**SYNOPSIS**	(For national authority use only)
Study Code	D8480C00002		
Date	17 September 2007		

A Phase I, Multi-centre, Two Part, Open Study to Assess the Safety and Tolerability of AZD2171 following Multiple Oral Doses in Patients with Relapsed or Refractory Acute Myeloid Leukaemia and Elderly Patients with *De Novo* or Secondary Acute Myeloid Leukaemia

Study dates		**Phase of development**
First patient enrolled	5 April 2004	Clinical pharmacology (I)
Last patient completed	14 December 2006	

Objectives

The primary objective of the study was to determine the safety and tolerability of multiple oral doses of AZD2171 in acute myeloid leukaemia (AML) patients by assessment of adverse events, blood pressure and pulse, heart rate, respiration rate, electrocardiogram, clinical chemistry, haematology, urinalysis and physical examination.

The secondary objectives were:

1. To confirm biological activity and investigate the minimum biologically active dose of AZD2171 by assessment of its effects on mean arterial pressure, bone marrow microvessel density and biological markers.

2. To characterise the pharmacokinetic profile at steady state by assessment of the following pharmacokinetic parameters: $C_{ss,max}$, $C_{ss,min}$, t_{max} and AUC_{ss}.

3. To determine the effect of AZD2171 on clinical response rate in a preliminary manner by assessment of changes from baseline in bone marrow and blood myeloblast count and cellularity.

Study design

This was an open, multi-centre study in 2 parts with multiple ascending dosing in Part A followed by a randomised, parallel-group cohort expansion phase (Part B), to determine the safety and tolerability of multiple oral doses of AZD2171 in acute AML. In the expansion phase (Part B) the maximum tolerated dose (MTD) together with a lower biologically active dose were to be explored.

Target patient population and sample size

Eligible patients were those with relapsed or refractory AML and elderly patients with *de novo* or secondary AML.

Approximately 30 patients were to be recruited into Part A of the study with a minimum of 3 patients at each dose level. Recruitment was to continue until up to 4 naive patients were entered into each cohort. If a patient withdrew for reasons other than a dose limiting toxicity (DLT), they were to be replaced until 3 evaluable patients (at least 2 naive) completed each cohort. In Part B of the study, 24 patients were to be randomised with 16 patients to receive doses of AZD2171 at the MTD and 8 patients at the lower biologically active dose level.

Dose-limiting toxicity

Dose-limiting toxicity was defined according to ECG and adverse event criteria:

- A single QTc (Bazett's correction) value of ≥550 msec or an increase of ≥100 msec from baseline[1].

Two consecutive ECG measurements, within 24 hours of one another, where either of the following criteria were met:

- both ECGs had a QTc interval ≥500 msec, but <550 msec
- both ECGs showed an increase of ≥60 msec from baseline QTc to a QTc value ≥460 msec.

DLT was defined as any other CTCAE grade 3 or higher toxicity that was considered possibly related to AZD2171 by either the Investigator or AstraZeneca physician, with the exception of isolated increases in γ -glutamyl transpeptidase, ie, in the absence of increases in transaminases.

[1] Baseline QTc was taken as the average of the screening and pre-dose assessments.

Investigational product: dosage, mode of administration and batch numbers

Patients received multiple daily oral doses of AZD2171 tablets indefinitely. The starting dose was selected prior to the first patient being entered onto the study and was based upon the available safety and tolerability data from the forerunner Study D8480C00001. Table S1 summarises the planned dose escalation strategy for Part A of the study.

Table S1 Dose escalation strategy for Part A

Dose Level	Dose of AZD2171 (mg)
Dose 1	5
Dose 2	7.5
Dose 3[a]	10
Dose 4	15
Dose 5	20
Dose 6	25
Dose 7	30
Dose 8	37.5
Dose 9	45

a Dose escalation was commenced at Level 3 following results obtained from Study D8480C00001.

Intra-patient dose escalation was permitted in Part A of this study and could occur after the current dose level had been declared tolerable and only once the patient has completed 22 days of continuous multiple dosing at their current dose level. Patients who had their dose increased received the new dose level that was being explored, unless due to a DLT, dose de-escalation was necessary in which case they would then only be able to increase their dose by one dose step.

If all patients within a dose level had not had a drug related toxicity greater than CTC grade 1 then dose escalation to the next dose level could occur once 3 patients had been followed for 14 days; this must include at least 2 patients who had not previously been exposed to a lower dose level. Once 1 patient within a dose level developed a drug related toxicity of CTC grade 2 or higher then dose escalation to the next dose level could occur when 3 patients had been followed for 21 days; again this must include at least 2 patients who had not previously been exposed to a lower dose level.

Doses were escalated by two dose levels (ie, dose level 1, 3, 5 etc) until 1 or more patients had experienced a DLT or if 2 or more patients have experienced drug related toxicity of CTC grade 2 or above. Thereafter, dose escalation was by single dose levels. However, if dose escalation in Study D8480C00001 (which was ongoing at the time this protocol was finalised), progressed more rapidly than in this study, greater increases than detailed above may be made up to a dose that is no greater than that currently proven to be tolerated in Study D8480C00001. Such increases in dose were subject to safety committee approval. If the MTD had not been reached by 45 mg, then additional doses could be administered at

increments of no more than 10 mg per dose step following a safety committee review of the available safety, pharmacokinetic and pharmacodynamic data.

In the Part B expansion phase, patients were randomised to 1 of 2 doses, the maximum tolerated dose (MTD) together with a lower biologically active dose.

AZD2171 was manufactured by AstraZeneca as brown, film-coated tablets and supplied by Investigational Products (IPS) at AstraZeneca, Macclesfield, UK. Tablets were packed into white high-density polyethylene (HDPE) bottles with child resistant, tamper evident closures. Multiple dosing bottles were provided with 35 tablets in each bottle. The details of the investigational product are given in Table S2.

Table S2 Details of investigational product and other study treatments

Investigational product or other treatment	Dosage form and strength	Manufacturer	Formulation number	Batch number(s)
AZD2171	2.5 mg tablets	AstraZeneca[a]	F12990	92613H02 10302C03 14101J03
AZD2171	10 mg tablets	AstraZeneca	F13012	10376G03 30488K05 32307D05 14102G03 22295H04

a Investigational Products Section at AstraZeneca, Macclesfield, UK.

Duration of treatment

Patients could continue 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 the therapy.

Variables

- **Pharmacokinetic**

  Following daily dosing with AZD2171 for 21 days: maximum steady state plasma concentration ($C_{ss,max}$), minimum steady state plasma concentration ($C_{ss,min}$), time to maximum plasma concentration (t_{max}), area under the plasma concentration-time curve during any dosing interval at steady state (AUC_{ss}).

- **Pharmacodynamic**

  Mean arterial blood pressure (MAP)[2], bone marrow microvessel density (MVD), receptor tyrosine kinase (RTK) expression (including VEGFR-2 [KDR], VEGFR-1 [Flt-1], VEGFR-3 [Flt-4], Flt-3, PDGFR-ß and c-Kit, but not excluding others) on leukaemic blasts and mRNA profiling, markers of activation (including phosphorylation of VEGFR-2, VEGFR-1, VEGFR-3, Flt-3, PDGFR-ß, c-Kit and downstream markers, but not excluding others) and markers of proliferation, markers of angiogenesis and activated endothelial cells.

- **Efficacy**

  Bone marrow and blood myeloblast counts and bone marrow cellularity.

- **Pharmacogenetics**

  Optional samples were taken for retrospective genotyping of known genes of the vascular endothelial growth factor (VEGF) and VEGF Receptor (VEGFR) system and other genes that may be involved in the response to AZD2171 and for mutation analysis in genes known to be mutated in AML (ie, c-Kit).

- **Safety**

  Adverse events, blood pressure (BP) and pulse, heart rate (HR), respiration rate (RR), electrocardiogram (ECG), clinical chemistry, haematology, urinalysis, physical examination.

Statistical methods

A patient's remission status was classified as complete response (CR), morphological response (MpR)[3], partial response (PR), minor response (MnR), stable disease (SD) or progressive disease (PD) as defined in Cheson (Cheson *et al* 2003).

Pharmacokinetic-pharmacodynamic models were fitted to explore the relationship between surrogate markers of activity (systolic blood pressure, diastolic blood pressure and VEGF) and PK parameters of AZD2171 plasma exposure (AUC_{ss} and $C_{ss,max}$), for Part A, Part B and Parts A and B combined.

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[2] At the time this protocol and study were commenced, an effect of AZD2171 on blood pressure became clear in a study that was in the process of reporting (D8480C00001). In study D8480C00001 mean arterial blood pressure was examined as a proof of principle marker of drug activity. In this study, it was later considered unnecessary to examine MAP in this way in preference to systolic and diastolic blood pressures that are regarded as more meaningful clinical measures. Mean arterial blood pressure (MAP) has only been listed for individual patients.

[3] Morphological response (MpR) as referred to in this CSR, is taken to mean morphologic complete remission with incomplete blood count recovery (CRi), (Cheson *et al* 2003).

Part A and Part B of the study have been considered separately. All patients are included in the analysis according to the treatment received. Data from the patients who withdrew from the study, or who have missing values for other reasons, are included in the analysis in such a way as to minimise any possible bias. A strategy for dealing with protocol deviations was agreed by the investigator, study team physician, pharmacokineticist and statistician as part of the SAP prior to database lock.

In part A of the study intra-patient dose escalation was permitted. In summarising data from such patients the following rules were applied:

- All baseline data was summarised by initial dose received.
- All post-baseline data that could only occur once (eg death) was summarised by the maximum dose taken prior to the event.
- All other post-baseline data was summarised by the maximum dose taken prior to the data, however patients could then be included in more than one treatment cohort in these summaries (for example, a patient escalating from 20mg to 30mg would have data recorded before the escalation summarised as 20mg, and data after the escalation summarised as 30mg) and were included in the total column once for each cohort.

Patient population

In total, 49 patients were enrolled into the study and of these 35 patients were dosed. In Part A, 23 patients received AZD2171 in 3 Cohorts: 10 mg Cohort (4), 20 mg Cohort (6) and the 30 mg Cohort (13). In Part B, 12 patients received study drug with 9 patients at the MTD (30 mg) and 3 at the lower biologically active dose level (20 mg). The first patient was enrolled on 5 April 2004 and the last patient completed the study on 14 December 2006. Fourteen patients did not receive AZD2171 due to failure to meet entry criteria.

Patient recruitment to Part B of the study was slower than anticipated and during September 2006, the study team decided to undertake a review of the available data supporting the secondary objectives assessing the biological activity of AZD2171. Examination of data from 9 evaluable patients provided evidence of considerable difficulties confirming either decreases in MVD or changes in the studied biomarkers. This is described more fully in the study conclusions. The study team concluded that recruitment would need to be substantially increased together with potential changes to patient entry criteria in order to address these findings. After careful consideration, the decision taken by the team was that the further recruitment to Part B should be stopped. The study had met its primary objective and provided further safety information for AZD2171.

All 35 (100%) patients had discontinued from the study as of the date of database lock. The most common reason for the permanent discontinuation was worsening of the condition under investigation (21 [60.0%] patients). Death due to a fatal adverse event was the reason for 4 (11.4%) patients discontinuing; in each case the secondary cause of death was reported as AML. A further 4 (11.4%) patients discontinued due to non-fatal adverse events. Other

reasons for discontinuing the study were 'patient not willing to continue the study' (3 [8.6%]), 'no response' 2 (5.7%) and 'increased level of leucocytosis' 1 (2.9%), see Table S3.

Table S3 Patient disposition by initial dose of AZD2171

Disposition	Number (%) of patients							
	Part A				Part B			A+B
	10 mg N=4	20 mg N=6	30 mg N=13	All doses N=23	20 mg N=3	30 mg N=9	All doses N=12	All doses N=35
Enrolled[a]	-	-	-	-	-	-	-	49
Allocated study drug	4 (100.0)	6 (100.0)	13 (100.0)	23 (100.0)	-	-	-	-
Randomised[b]	-	-	-	-	3 (100.0)	9 (100.0)	12 (100.0)	-
Received study drug	4 (100.0)	6 (100.0)	13 (100.0)	23 (100.0)	3 (100.0)	9 (100.0)	12 (100.0)	35 (100.0)
Discontinued study:								
Condition under investigation worsened	2 (50.0)	4 (66.7)	9 (69.2)	15 (65.2)	1 (33.3)	5 (55.6)	6 (50.0)	21 (60.0)
Adverse event	0 (-)	2 (33.3)	1 (7.7)	3 (13.0)	0 (-)	1 (11.1)	1 (8.3)	4 (11.4)
Patient not willing to continue study	0 (-)	0 (-)	2 (15.4)	2 (8.7)	0 (-)	1 (11.1)	1 (8.3)	3 (8.6)
Other:								
Death	2 (50.0)	0 (-)	0 (-)	2 (8.7)	0 (-)	2 (22.2)	2 (16.7)	4 (11.4)
Increased level of leucocytosis	0 (-)	0 (-)	0 (-)	0 (-)	1 (33.3)	0 (-)	1 (8.3)	1 (2.9)
No response	0 (-)	0 (-)	1 (7.7)	1 (4.3)	1 (33.3)	0 (-)	1 (8.3)	2 (5.7)

a Enrolled patients who were not allocated drug (in Part A) or randomised in Part B are identified in Appendix 12.2.4.2, together with the reason for ineligibility.
b In Part B patients were randomised to receive either the MTD or the lower biologically active dose level.

There were no important differences between the dose cohorts in Part A or B of the study for the demographic characteristics of the studied patients. The study population was Caucasian (100%), with a mean (SD) age of 67.7 (6.6) years (age distribution: 31% of patients were 18 to <65 years, 49% of patients were ≥65 to <75 years and 20% were ≥75 years of age).

For 17 (48.6%) patients AML was reported as *de novo* with 15 (42.9%) as secondary to myelodysplastic syndrome, 2 (5.7%) as secondary to chemotherapy and for 1 (2.9%) patient, AML type was unknown. For AML status, 13 (37.1%) patients were newly diagnosed, 9 (25.7%) were reported as refractory AML, 10 (28.6%) with a first relapse in AML and 3 (8.6%) with a second relapse. The majority of patients were FAB M1, M2 or M4 (accounting for approximately 70% of the studied population).

Twenty-five (71%) patients were positive for the c-Kit protein (CD117). Of the remaining patients, 5 (14%) were negative and 5 (14%) had no test results (ie, were not recorded or performed). The proportion of patients with positive results for c-Kit was >50% in each dose

cohort (range 54 to 100%). The study population included some patients with both good and poor prognostic cytogenic profiles at baseline: 2 (6%) had complex cytogenetics (ie, >3 abnormalities) and 1 (3%) patient had abnormalities of 5 or 7; these abnormalities are associated with a poorer outcome in AML studies. This compared with 2 (6%) patients with inv 16 and 1 (3%) with t (8; 21) that are associated with a more favourable prognosis. Of the remainder of the patients, 23 (66%) had 'other' chromosomal abnormalities and 6 [17%]) had no test results ie, were not recorded or a sample was not available.

Sixteen (46%) patients were Flt-3-positive and 2 (6%)were negative by flow cytometry analysis; the remainder, (17 [49%]) had no test results (ie, were not recorded or performed). The proportion of patients with positive results for Flt-3 was >31% in each dose cohort (range 31 to 75%). Five patients (14%) had an internal tandem duplication mutation [ITD] of Flt-3, detectable by DNA analysis: 3 (23%) in the 30 mg cohort (Part A) and in Part B, 1 (13%) patient in the 20 mg cohort and 1 (11%) in the 30 mg cohort. The ITD mutation has been associated with a poorer outcome in previous studies in AML. For the remaining patients 26 (74%) had Wild-type Flt-3 and in 4 [11%]), the sample for DNA analysis was not available or the result not recorded. Of 15 (43%) patients who were tested for VEGFR-2 by flow cytometry, none were VEGFR-2 positive. For the remaining patients (20 [57%]), the sample was not performed or the result not recorded.

Treatment compliance, calculated as actual dose of study drug whilst in a cohort, taking into consideration dose reduction and interruptions, was good in each dose cohort (mean dose intensity 91.5 to 100%), with an overall mean (SD) of 95.4% (11.5%).

The treatment groups were comparable at baseline for concomitant medications, except for medications that may affect hypertension taken prior to study entry. An explanation for the difference between the dose cohorts may be the small number of patients in the 10 mg (Part A) and 20 mg (Part B) cohorts with 4 and 3 patients, respectively. The proportion of patients taking medications that may affect hypertension after study entry was similar in the 10, 20 mg and 30 mg cohorts in Part A with 50, 44.4 and 53.3%, respectively and similar to the 30 mg cohort in Part B (44.4%). In the 20 mg cohort (Part B) there were no patients taking these medications after study entry.

Although there were patients who met the criteria for a protocol deviation, none of them were excluded from the final analyses.

Maximum tolerated dose (primary objective)

The proportion of patients reporting DLTs at the time of ongoing safety assessment during periodic reviews (relative to recruitment and cohort expansion, taking into consideration patient evaluability) meant that escalation to a dose level >30 mg was not allowable (ie, in accordance with the protocol). Furthermore, the 30 mg dose cannot be declared non-tolerated (ie, where >50% of patients report DLT) or well tolerated (ie, where <33% report DLT). These results are fully described below.

In Part A of the study, 4 patients received 10 mg of AZD2171 with no DLTs and the study was continued to the next dose level (20 mg). In Part A, 9 patients received 20 mg of AZD2171 (6 naïve to AZD2171 and 3 patients who were escalated from the 10 mg cohort). There was 1 report of a DLT in this cohort, CTC grade 3 *Palmar-plantar erythrodysaesthesia syndrome* on Day 8 that was assessed by the investigator to be causally related to AZD2171. The study was continued to the next dose level (30 mg).

In total, 15 patients received 30 mg of AZD2171: 13 naïve to AZD2171 and 2 patients who were escalated from the 20 mg cohort[4].

The DLTs reported in the final evaluation of 30 mg cohort were as follows:

- Patient E0004999 reported a DLT (CTC grade 3) of *Electrocardiogram QT corrected interval prolonged* on Day 9. AZD2171 was temporarily stopped and then restarted at 20 mg. The patient was then withdrawn 1 week later because of disease progression. This DLT was not substantiated by independent cardiology ECG assessment. This patient also reported *hypertension* (CTC grade 3) as a DLT on Day 15.

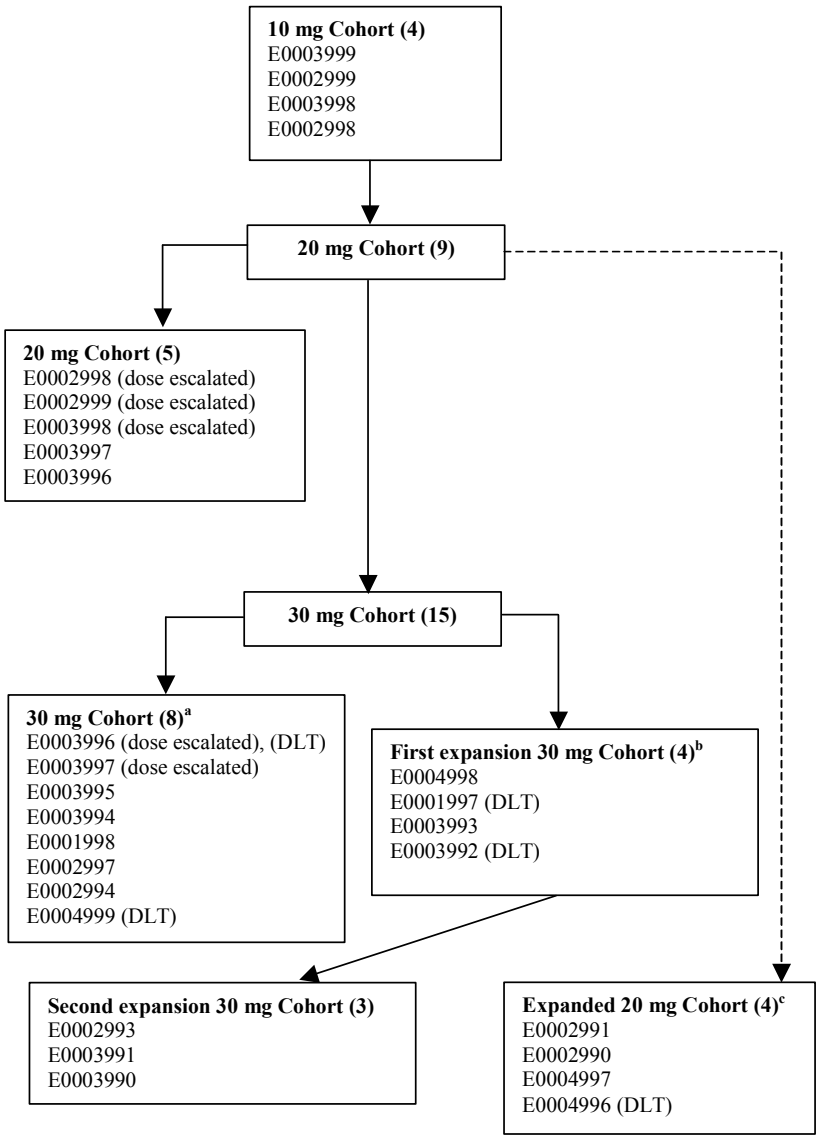
- Patient E0001997 reported a DLT (CTC grade 3) of *hypertension* on Day 1. AZD2171 was permanently stopped and the patient was withdrawn from the study on Day 8.

- Patient E0003992 reported a DLT (CTC grade 3) of *diarrhoea* on Day 6. AZD2171 was temporarily stopped and then restarted at 20 mg.

Dose escalation in Part A of the study in presented in Figure S1.

[4] Of the first 8 patients in the 30 mg cohort, 5 were evaluable for assessment of dose tolerability; 3 patients had insufficient exposure to AZD2171 (E0003995, E0003994 and E0001998). Of the evaluable patients in the initial cohort of 8, 2 patients reported DLTs: E0003996 (*Dry mouth*) and E0004999 (*Electrocardiogram QT corrected interval prolonged*) ie, 40% of evaluable patients reported DLTs. The 30 mg dose could not be declared non-tolerated until >50% of patients reported DLTs and therefore the cohort was expanded. Once a cohort is expanded, safety information from patients who were escalated from a lower dose are no longer considered in any future assessment of non-tolerability eg, patient E0003996, see also Figure S1.

Figure S1 Dose escalation in Part A of the study



a Of the first 8 patients in the 30 mg cohort, 5 were evaluable for assessment of dose tolerability: 3 patients had insufficient exposure to AZD2171 (E0003995, E0003994 and E0001998). Of the evaluable patients in the initial cohort of 8, 2 patients reported DLTs: E0003996 (*Dry mouth*) and E0004999 (*Electrocardiogram QT corrected interval prolonged*) ie, 40% of evaluable patients. The 30 mg dose could not be declared non-tolerated until >50% of patients reported DLTs and therefore the cohort was expanded.

b Once a cohort is expanded, safety information from patients who were escalated from a lower dose are no longer considered in any future assessment of non-tolerability ie, within the expanded cohort (eg, patient E0003996). In the expanded cohort, the DLTs that were relevant were those reported for patients E0004999 (*Electrocardiogram QT corrected interval prolonged*), E0001997 (*Hypertension*) and E0003992 (*Diarrhoea*), ie, 3 of 6 patients (50%) reported DLTs. Again, the 30 mg dose could not be declared non-tolerated (ie, where >50% of patients reported DLTs) and the cohort was expanded one final time. In the second and final expansion, none of the 3 patients reported DLTs giving an overall rate of 3:9, ie, 33%.

c The study team decided to expand the 20 mg cohort following the experience obtained after the first expansion of the 30 mg cohort to further examine the tolerability of this dose and prior to its nomination as the lower dose for Part B of the study. A further 4 patients were dosed with one patient from this expansion reporting a DLT: E0004996 (*Palmar-plantar erythrodysaesthesia syndrome*).

Summary of pharmacokinetic results

Plasma concentrations reached their maximal value from 0.83 to 4.3 hours post dosing for all dose levels. Visual inspection of the pre-dose (trough) plasma concentration values supports that steady-state plasma concentrations are attained after approximately 7 days of repeated once daily dosing. The ratio of geometric mean for $C_{ss,max}$ to $C_{ss,min}$ was approximately 3 for all dose levels supporting constancy in plasma exposure at steady-state, see Table S4. The PK parameter estimates for the 20 mg and 30 mg dose levels are similar in both parts of the study (see Table S5).

Table S4 Pharmacokinetic parameters of AZD2171 following 21 days of once-daily dosing (10 mg to 30 mg) in Part A

Parameter (units)	Summary statistics	Dose of AZD2171		
		10 mg N[a]=4	20 mg N=6[b]	30 mg N=13[c]
AUC_{ss} (ng/mL*hr)	gmean (CV%)	323 (70.3)	358 (81.9)	810 (26.2)
$C_{ss,max}$ (ng/mL)	gmean (CV%)	22.8 (53.2)	25.4 (61.3)	61.0 (46.7)
$C_{ss,min}$ (ng/mL)	gmean (CV%)	9.19 (66.5)	8.67 (164)	22.1 (34.6)
t_{max} (h)	Median (range)	1.5 (1.0 to 2.9)	3.2 (2.0 to 4.3)	2.2 (0.83 to 4.1)

a 'N' is the number of patients in each cohort.
b In the 20 mg cohort, 4 patients provided evaluable data for each parameter.
c In the 30 mg cohort, 8 patients provided evaluable data for $C_{ss,max}$ and t_{max}, and 6 for $C_{ss,min}$ and AUC_{ss}.

Table S5 Pharmacokinetic parameters of AZD2171 following 21 days of once-daily dosing (20 mg and 30 mg) in Part B

Parameter (units)	Summary statistics	Dose of AZD2171	
		20 mg N[a]=3[b]	30 mg N[a]=9[c]
AUC_{ss} (ng/mL*hr)	gmean (CV%)	424 (1.0)	745 (94.2)
$C_{ss,max}$ (ng/mL)	gmean (CV%)	32.7 (35.7)	65.4 (80.2)
$C_{ss,min}$ (ng/mL)	gmean (CV%)	8.74 (52.7)	20.4 (62.6)
t_{max} (h)	Median (range)	3.0 (2.0 to 4.0)	3.0 (0.92 to 3.3)

a 'N' is the number of patients in each cohort.
b In the 20 mg cohort, 2 patients provided evaluable data for each parameter.
c In the 30 mg cohort, 5 patients provided evaluable data for $C_{ss,max}$ and t_{max}, and 4 for $C_{ss,min}$ and AUC_{ss}.

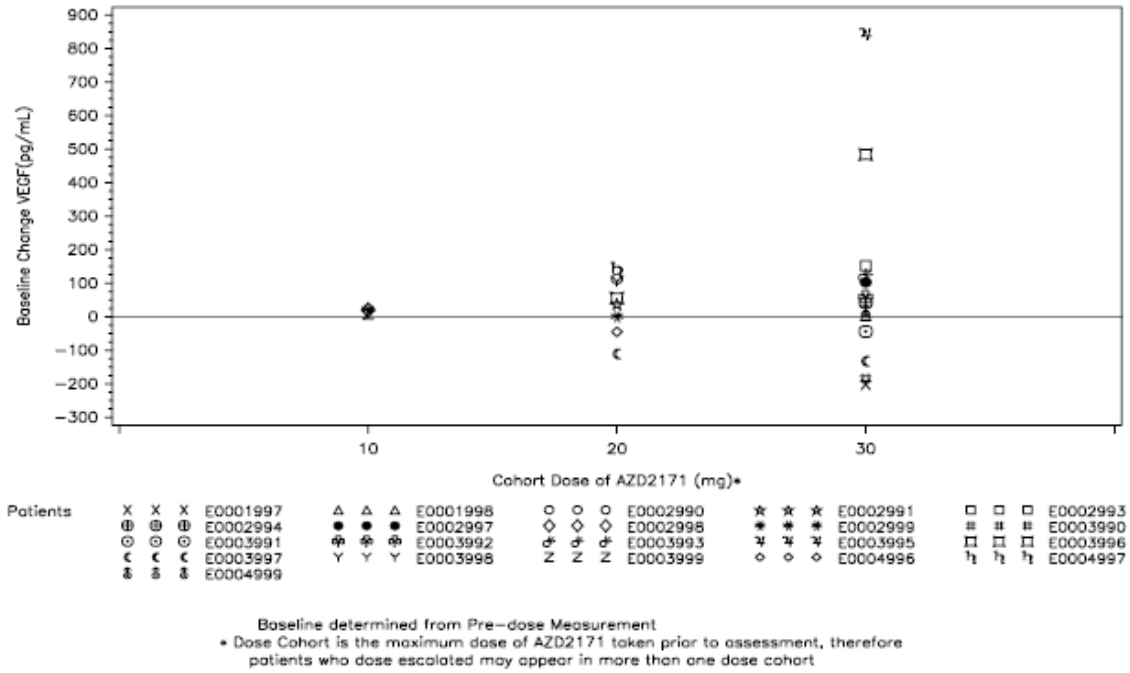
Summary of pharmacodynamic results

It was hypothesised that reductions in bone marrow microvessel density (MVD) may be observed on treatment with AZD2171 with the potential to confirm biological activity and investigation of the minimum biologically active dose of AZD2171.

The results appeared variable and for the majority of patients data were only available for only 2 or 3 time-points. Therefore it was difficult to establish whether or not there was a dose relationship and changes during the duration of treatment.

Soluble markers of angiogenesis and activated endothelial cells: There was no clear evidence of a treatment related effect on plasma VEGF levels in this study, in contrast to a previous study with AZD2171 (Study D8480C00001), see Figure S2.

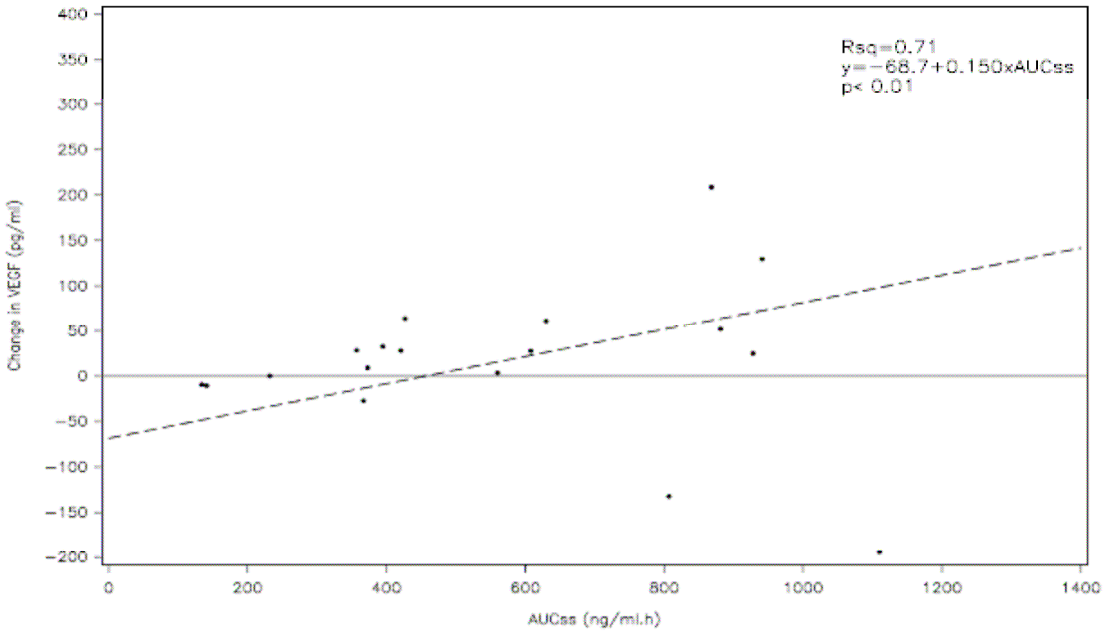
Figure S2 Mean within-patient change from baseline for VEGF (pg/mL), Part A, (Day 8 onwards)



Baseline determined from Pre−dose Measurement
* Dose Cohort is the maximum dose of AZD2171 taken prior to assessment, therefore patients who dose escalated may appear in more than one dose cohort

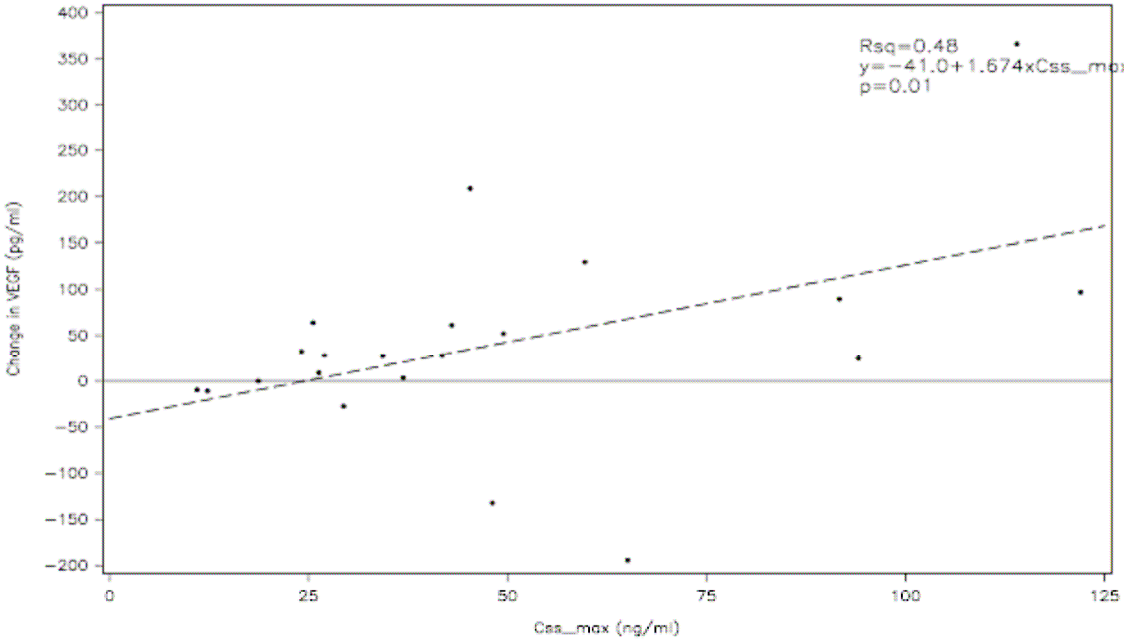
However, there was a strong correlation with VEGF levels and AZD2171 PK, both AUC_{ss} and $C_{ss,max}$ (see Figure S3 and Figure S4).

Figure S3 Relationship between change in VEGF and AUC_{ss} (Parts A and B combined, Day 22)



VEGF values below the minimum level of detection are treated as half the minimum level of detection in the plot

Figure S4 Relationship between change in VEGF and $C_{ss,max}$ (Parts A and B combined, Day 22)

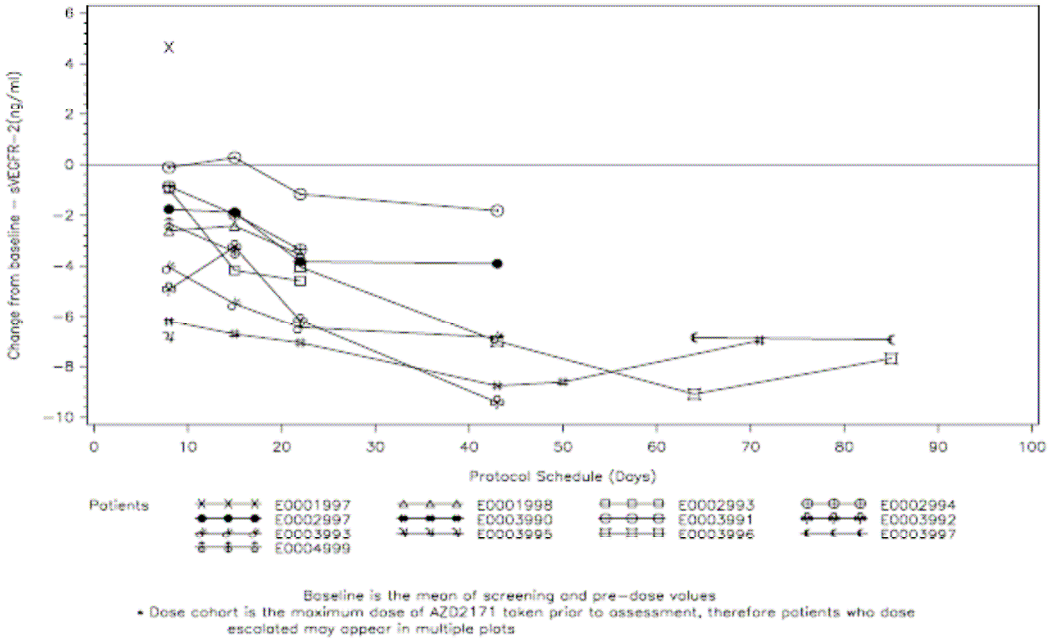


VEGF values below the minimum level of detection are treated as half the minimum level of detection in the plot

Time dependent changes in sVEGFR-2 levels were observed, consistent with other studies of AZD2171 (see Figure S5). There were no treatment-related changes in plasma levels of any of the following markers of angiogenesis: bFGF, sE Selectin, sFlt-1, Tie-2 and IL-8.

RTK (receptor tyrosine kinase) expression and activation status on leukaemic blast cells: The RNA expression of Flt -3 and c-Kit was high in all patients but the levels of expression of the VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β and FGFR-1, was very low at baseline in this patient group. No treatment related changes in expression of any of the receptors at the RNA level were observed. The analysis of receptor tyrosine kinase expression and activation on protein level (Flt-3, c-Kit, VEGFR-2) in bone marrow, in samples obtained in Parts A and B of the study, was inconclusive. The blood samples did not contain sufficient numbers of leukaemic blast cells to enable analysis. In the bone marrow samples the expression of the specific markers at baseline were low or not detectable in the majority of cases, therefore detection of treatment related changes was not possible in the majority of cases.

Figure S5 Time profiles for sVEGFR-2 (ng/mL) Days 1-100 (change from baseline), Part A (30 mg dose cohort)



Leukaemic blast proliferation status: Detection of phosphorylated histone H3 (phH3) by immunohistochemistry (IHC) in bone marrow trephine samples was used as an indicator of the proliferation status of the leukaemic blasts. There was no clear evidence of a dose-dependent change in proliferation status during the study using this marker.

Summary of pharmacokinetic/pharmacodynamic correlations

There was not a readily apparent relationship between the change from baseline in SBP or DBP and both AUC_{ss} and $C_{ss,max}$.

The PK-PD relationship between the change from baseline in VEGF and AUC_{ss} for Parts A and B (combined) was significant ($p< 0.01$) and strong (R-square 0.71) and the relationship between the change from baseline in VEGF and $C_{ss,max}$ was also significant ($p= 0.01$) and strong (R-square 0.48). A significant and strong relationship was also observed when the data from Part A was examined alone for $C_{ss,max}$ and AUC_{ss}. However, when the data from Part B was examined alone the relationships for AUC_{ss} and $C_{ss,max}$ were weak and not significant.

Summary of population pharmacokinetics

A population PK modelling analysis of the plasma concentration time course data, the population PK structure, covariate effect, and residual error models, together with the estimated population mean and inter-patient variability (if applicable) for the corresponding model parameters, if reported, will be in a separate document to this CSR.

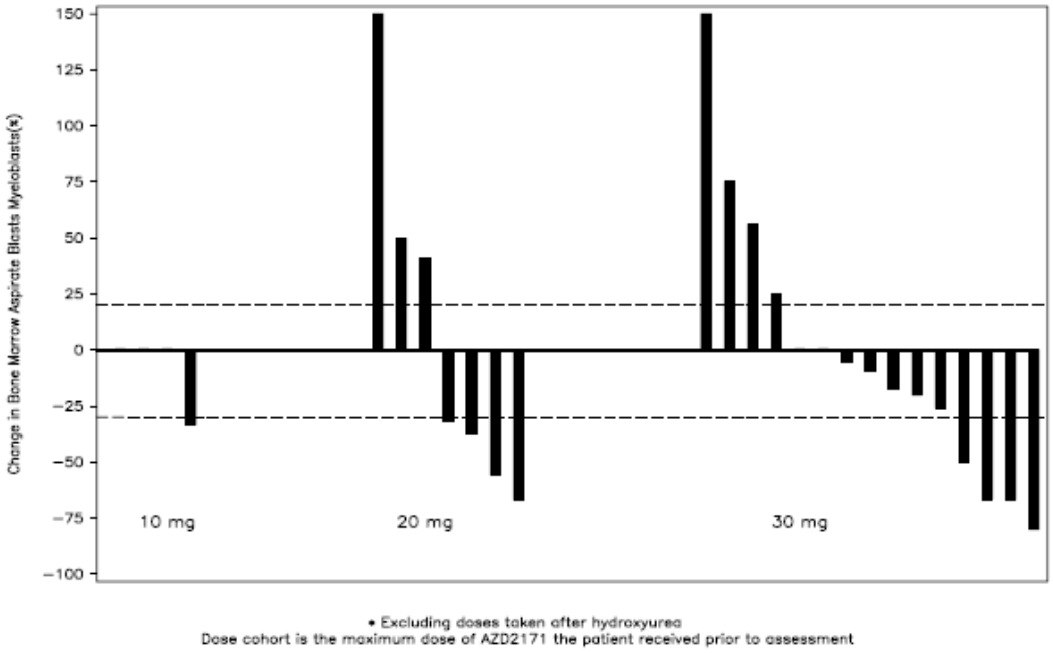
Summary of pharmacogenetics

Although samples were collected for retrospective genotyping, no analyses had been performed or were planned at the time of preparing this CSR.

Summary of efficacy

Preliminary evidence of anti-leukaemia activity was observed at doses of AZD2171 20 mg and 30 mg. The data also show that investigator-reported responses better than SD, were observed at doses of AZD2171 20 mg and 30 mg in Part A (ie, partial, minor and morphological responses). In the 20 mg cohort 2 patients were reported with PR and 1 with MnR (a reduction in bone blast cells to <75% pre-treatment value). In the 30 mg cohort 2 patients were reported with PR and 1 patient with morphological response (MpR). A waterfall plot of smallest post-dose percentage change in bone marrow aspirate blasts (Parts A and B) for all data up to Day 21 indicated a reduction in bone marrow aspirate blasts for the majority of patients, however there were too few patients per cohort to confirm any dose relationship (Figure S6).

Figure S6 Waterfall plot of smallest post-dose percentage change in bone marrow aspirate blasts (Parts A and B), all data up to Day 21



Summary of other safety results

Mean (SD) actual exposure to AZD2171 (all dose cohorts) was in the range 27.9 (15.1) to 139.2 (159.6) days and was highest in the 20 mg cohort (Part A) at 139.2 (159.6) days with few dose reductions/interruptions.

During the study 97.5% patients experienced 1 or more AEs and of these, 52.5% patients experienced an AE that was considered by the investigator to be related to treatment. The proportion of patients reporting any AE was similar in each cohort (Parts A and B). In total, 25 (62.5%) patients had an AE of CTC grade 3 or higher and for 7 (17.5%) patients the AE was related to treatment.

There were 5 (14.3%) deaths due to an AE, all unrelated to AZD2171. Approximately 60% of patients reported SAEs with 3 (7.5%) patients reporting treatment related SAEs as assessed by the investigator. The most commonly reported SAE (all doses combined) was *pyrexia* (7 [17.5%]), an unsurprising finding in an AML population. None of these events were assessed causally related to AZD2171. Other SAEs were reported at low incidence: *fatigue* by 3 (7.5%) patients, with all other SAEs by ≤2 patients per preferred term, (all doses combined).

Few patients experienced DAEs (4 [11.4%]) with 3 (13.0%) in Part A and 1 (8.3%) in Part B of the study, for 2 (5.7%) patients the DAE was related to treatment: *palmar-plantar erythrodysaesthesia syndrome* (20 mg cohort) and *hypertension* (30 mg cohort).

Diarrhoea was the most frequently reported OAE with 19 (47.5%) patients (all doses combined), followed by hypertension for 15 (37.5%) patients: *hypertension* 14 (35%) patients

together with 2 (5%) patients who reported *hypertonia* (arterial hypertension) in the 20 mg cohort (Part A); patient E0004997 reported both *hypertension* and *hypertonia*.

The most commonly reported AEs were *diarrhoea*, *hypertension* and *fatigue*. These events occurred across all of the doses investigated. There were few causally related AEs reported at an incidence of ≥5% (all cohorts combined). The most commonly reported causally related AE from the combined data was *diarrhoea* CTC Grade 1 (8 [20%] patients) and *hypertension* CTC Grade 2 (6 [15%]). Overall, the incidence in the reporting of causally related AEs appeared to increase with dose.

Although the majority of patients in this study experienced clinical laboratory abnormalities, there were no clinically important trends in laboratory parameters over time. Dose-related increases in TSH were observed at doses of 20 mg and 30 mg that were consistent with findings from another study (D8480C00001). No new issues were identified for AZD2171 from the available clinical laboratory results.

Dose-related increases in blood pressure were observed at AZD2171 doses of 20 mg and 30 mg. However, the majority of these patients had relevant past medical histories and several were receiving medication for hypertension at baseline. There were no apparent treatment related changes for the ECG data obtained in this study.