AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1152
Study Code	D1531C00007
Edition Number	1
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A Phase I/II, Open-Label, Multi-centre, 2-part study to assess the Safety, Tolerability, Pharmacokinetics and Efficacy of AZD1152 in Patients with Acute Myeloid Leukaemia

Study dates: First patient enrolled: 23 May 2006
Last patient enrolled: 23 February 2009

Phase of development: Clinical pharmacology (I)/Therapeutic exploratory (II)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

This study was conducted at 11 centres in 4 countries (Netherlands [4 centres], France [3], Italy [2] and the United States of America [2]).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary: Dose escalation phase (Part A)	**Primary**	
To assess the safety and tolerability of multiple ascending doses of AZD1152 in patients with AML by assessment of AEs, vital signs, ECG parameters, clinical chemistry, haematology (including clotting parameters) and urinalysis.	Assessment of AEs, vital signs, ECG parameters, clinical chemistry, haematology (including clotting parameters) and urinalysis.	Safety
Primary: Expansion phase at the MTD (Part B)	**Primary**	
To assess the effect of AZD1152 on the rate of CR in patients with AML, with CR defined by changes from baseline in bone marrow and blood myeloblast counts and recovery of normal haemopoiesis.	Rate of CR, as defined by changes from baseline in bone marrow and blood myeloblast counts and recovery of normal haemopoiesis.	Efficacy
Secondary: Both phases (Part A and Part B)	**Secondary**	
To determine the PK of AZD1152 hQPA, and if possible AZD1152, from the observed concentration-time profiles by analysis of non-compartmental PK parameters which, depending on the data, could include C_{max}, AUC, $AUC_{(0-t)}$, t_{max}, $t_{1/2}$ and CL.	Analysis of non-compartmental PK parameters which, depending on the data could include C_{max}, AUC, $AUC_{(0-t)}$, t_{max}, $t_{1/2}$ and CL.	PK
To investigate the effect of AZD1152 on the levels of leukaemic blasts in blood samples by analysis of biomarkers of inhibition of Aurora kinase activity and other biomarkers of activity.	Analysis of leukaemic blasts from blood for biomarkers of inhibition of Aurora kinase activity.	PD
To explore the relationship between plasma concentrations and/or exposure of AZD1152 hQPA and AZD1152 with effects on biomarkers and/or safety parameters, using a graphical approach and/or appropriate PK/PD modelling techniques.	Investigate using a graphical approach and/or appropriate PK/PD modelling techniques, possible relationships between systemic drug concentrations/exposure and changes in PD and/or safety parameters.	PK/PD
Secondary: Expansion phase at the MTD (Part B)	**Secondary**	
To assess the effect of AZD1152 on durability of CR.	Durability of CR Durability of CR was assessed as the time from documented remission to: -Time of study endpoint (completion of 6-month follow-up or withdrawal) where remission persisted -Time to relapse.	Efficacy

Objectives	Outcome variables	Type
Secondary: Expansion phase at the MTD (Part B)	**Secondary**	
To assess the effect of AZD1152 on rate and durability of CRi, PR and overall response (CR+CRi+PR).	Rate and durability of CRi, PR and overall response (CR+CRi+PR). Durability of CR and CRi as above. Durability of PR was not calculated, as there is no clear definition of relapse for patients already experiencing a PR.	Efficacy
To further assess the safety and tolerability of multiple doses of AZD1152 in patients with AML by assessment of AEs, vital signs, ECG parameters, clinical chemistry, haematology (including clotting parameters) and urinalysis.	Assessment of AEs, vital signs, ECG parameters, clinical chemistry, haematology (including clotting parameters) and urinalysis.	Safety

AE Adverse event; AML Acute myeloid leukaemia; AUC Area under plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$ Area under plasma concentration-time curve from zero to time t; AZD1152 hQPA AZD1152 hydroxy-quinazoline pyrazole anilide; CL Total body clearance of drug from plasma; C_{max} Maximum plasma concentration; CR Morphological complete remission (defined as all of the following: a decrease in bone marrow blasts to <5% total bone marrow nucleated cells demonstrated in bone marrow aspirate with adequate cellularity or a bone marrow trephine biopsy with >20% cellularity; disappearance of blasts from the peripheral blood; neutrophils ≥1.0 x 10^9/L; platelets ≥100 x 10^9/L; no extramedullary leukaemia; absence of Auer rods and transfusion-independent); CRi Morphological complete remission with incomplete blood count recovery (as for CR but with incomplete neutrophil or platelet recovery); ECG Electrocardiogram; MTD Maximum tolerated dose; PD Pharmacodynamic; PK Pharmacokinetic; PR Partial remission (a reduction in bone marrow blast cells of >50% to between 5% to 25%, or a reduction in bone marrow blast cells to <5% but with persistence of Auer rods); t_{max} Time to reach peak or maximum concentration; $t_{1/2}$ Half-life (terminal elimination).
Note: There was 1 tertiary objective (PD relationships); no data are presented in the clinical study report. In addition, as the actual duration of response was calculated for all but 1 patient; the term "duration" is used instead of "durability" hereafter.

Study design

An open label, non-randomised, multicentre, 2-part study designed to determine the maximum tolerated dose (MTD) of AZD1152 in patients with acute myeloid leukemia (AML), when administered as a continuous 7-day infusion every 21 days (7 days treatment and 14 days off treatment). The study was also designed to characterise the safety and tolerability, and pharmacokinetics (PK) and biological activity profiles of AZD1152.

In the Phase I, multiple ascending dose escalation phase (Part A), cohorts of a minimum of 3 patients received escalating doses of AZD1152 until the non-tolerated dose was reached. Dose escalation to the next dose occurred once 3 evaluable patients were followed for 21 days. If a dose limiting toxicity (DLT) occurred, the cohort was expanded to 6 evaluable patients. A patient was evaluable if they received ≥80% of the total AZD1152 dose over 7 days and completed the required safety visits for Cycle 1 or had a DLT. The Phase II expansion phase at the MTD (Part B) was designed to assess the effect of the AZD1152 MTD (determined in the dose escalation phase [Part A]) on the rate of morphological complete remission (CR) in patients with AML.

Target subject population and sample size

In the dose escalation phase (Part A), patients ≥18 years of age with relapsed or refractory AML for which no standard therapies were anticipated to result in durable remission were eligible. Patients with newly diagnosed AML who were not considered to be suitable for standard induction and consolidation chemotherapy for medical, social or psychological

reasons were also eligible. In the expansion phase at the MTD (Part B), patients ≥18 years of age with relapsed or refractory AML, for which no standard therapies were anticipated to result in durable remission (patients in first relapse were to have relapsed at least 1 month after an initial complete remission) or patients with newly diagnosed AML, who were not considered to be suitable for standard induction and consolidation chemotherapy for medical, social or psychological reasons, were eligible. The study was expected to recruit 45 to 60 patients, dependent on the number of dose escalation steps. It was anticipated that approximately 30 patients would be recruited into the dose escalation phase (Part A). For the expansion phase at the MTD (Part B) the target number of evaluable patients was 30 (maximum), of which 15 were to have been in first relapse.

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

Table S2 Details of investigational product

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Analytical Development Macclesfield number
Diluent	Diluent, 5 mL, continuous 7-day infusion, intravenous	AstraZeneca	F13412	33317D05, 43675H06, 41295A06
AZD1152	Lyophile, 100 mg, continuous 7-day infusion, intravenous	AstraZeneca	F13353	32929D05, 43746A06, 50757H07, 51295E07, 51296B07, P7974.

Duration of treatment

AZD1152 was administered as a continuous 7-day infusion, starting on Day 1 (0 hours) and finishing on Day 8 of a 21-day cycle. Patients in the dose escalation phase (Part A) were to receive at least 1 cycle of treatment, with the intention of receiving up to 2 further cycles of treatment, if their clinical condition permitted. Patients could continue with treatment if in the opinion of the investigator they were continuing to receive benefit. Patients in the expansion phase at the MTD (Part B) were to receive 3 cycles of treatment, although could continue with treatment if in the opinion of the investigator they were continuing to receive benefit.

Statistical methods

No formal statistical hypothesis testing was performed on the data from the dose escalation phase (Part A). All safety, tolerability, PK and pharmacodynamic (PD) data relating to each dose level and dosing period (ie, Part A or Part B) were listed and summarised for all patients. The analysis population for efficacy included all patients who received treatment with AZD1152. The primary outcome variable of the rate of CR was calculated. In addition, the secondary outcome variables of the rate of morphological complete remission with incomplete blood count recovery (CRi), partial remission (PR) and overall response (CR+CRi+PR) were calculated. The 80% confidence intervals (CIs) were estimated using the Wilson score method. Duration of response (for CR and CRi) was calculated from the date the response

was first observed to the date of relapse or death, or date of last available assessment for patients who withdrew from the study whist still in remission.

Subject population

A total of 64 patients received AZD1152 in this study; 32 patients in each phase (Part A and Part B). Dose escalation information is provided in Table S3.

Table S3 Dose escalation in Part A of the study

AZD1152 dose (n=patients)	Number of DLTs
50 mg (n=3)	No DLTs
100 mg (n=3)	No DLTs
200 mg (n=3)	No DLTs
400 mg (n=4)	No DLTs; the number of patients exceeded 3 due to co-incident patient recruitment.
800 mg (n=6)	One DLT of stomatitis (investigator text: oral mucositis) was reported in the first 3 patients and the cohort expanded to n=6 evaluable patients. Seven patients were treated as 1 patient was not evaluable (the patient did not receive ≥80% of the dose in Cycle 1).
1200 mg (n=6)	One DLT of stomatitis (investigator text: oral mucositis) was reported in the first 3 patients and the cohort expanded to n=6 evaluable patients. **Maximum tolerated dose (taken forward into expansion phase [Part B])**
1600 mg (n=6)	Two DLTs of stomatitis reported (investigator text: oral mucositis; oropharyngeal mucositis). **Non-tolerated dose**

DLT Dose limiting toxicity.

All but 1 of the 64 patients has discontinued the study; 1 patient was ongoing at data cut-off (14 October 2009). Thirty-five patients discontinued due to lack of therapeutic response and an additional 10 patients because the condition under investigation worsened. Eight patients discontinued due to death; 7 were due to disease progression and 1 due to a serious adverse event (SAE) of cerebral fungal infection (not related to treatment). Four patients discontinued the study due to an adverse event (AE). Five patients voluntarily discontinued the study and 1 patient discontinued the study for other reasons (wanted to go home).

The mean age of patients was 65.4 years and 68.4 years in the dose escalation phase (Part A) and expansion phase at the MTD (Part B), respectively. Thirty-two of the 64 patients were ≥60 to 70 years of age; 21 were ≥71 years of age. The majority of the 64 patients were male (37 patients) and Caucasian (62 patients). Twenty-four of the 64 patients had de novo AML, 23 patients had AML secondary to myelodysplastic syndrome, 7 of patients had AML secondary to chemotherapy and 1 patient had AML secondary to myeloproliferative disorder; 7 patients had AML reported as "Other" and data were missing for 2 patients. Thirty-seven of the 64 patients were in first relapse, 19 patients were newly diagnosed and 4 patients were in second relapse; information was missing for 4 patients. Fifteen of the patients recruited into expansion phase at the MTD (Part B) were to be in first relapse; however, it was only possible to recruit 12 patients. Cytogenetic data samples were available for 45 patients; 16 patients had

normal cytogenetics, 6 patients had complex karyotypes (>3 abnormalities), 7 patients had cytogenetic abnormalities of 5 and/or 7 and 1 patient had inversion 16 or t(16:16); 15 patients had cytogenetics listed as "Other". Sixty-one patients had received ≥1 course of chemotherapy and 5 patients had received prior radiotherapy.

Summary of efficacy results

The efficacy objectives related only to the expansion phase at the MTD (Part B); however, data were available and are presented for both phases. Sixteen responders (CR, CRi or PR) have been observed: CR (3), CRi (6) and PR (7). The CR+CRi rate was 14.1% (9 of 64 patients; 80% CI: 9.4 to 20.5) and CR+CRi+PR rate was 25.0% (16 of 64 patients; 80% CI: 18.7 to 32.5). Ten of the 38 patients at the MTD (1200 mg) had some form of a morphological response: CR (3), CRi (4) or PR (3); the CR+CRi rate was 18.4% (7 of 38 patients; 80% CI: 11.7 to 27.7) and CR+CRi+PR rate was 26.3% (10 of 38 patients; 80% CI: 18.3 to 36.3). Analysis by AML status showed of the 37 patients in first relapse, 5 patients had a CR or CRi (4 at the MTD). The durations of response for the 9 patients with a best response of CR or CRi were 7, 23, 23, 25, 27, 29, 58, 115 and 206 days (median 27 days). The duration of response was censored at 23, 27 and 115 days for 3 patients who withdrew from the study whilst still in remission, and at 206 days for 1 patient who was (ongoing and) still in remission at data cut-off.

Of the 16 patients with a best response of CR, CRi or PR, 11 patients responded after 1 cycle of treatment, 4 patients responded after 2 cycles and 1 patient responded after 3 cycles.

Summary of pharmacokinetic results

Following a 7-day infusion of AZD1152 from 50 mg to 1600 mg the exposure to AZD1152 hydroxy-quinazoline pyrazole anilide (hQPA) increased with dose in an approximately dose proportional manner. Plasma concentrations of AZD1152 and AZD1152 hQPA reached a plateau by the time of the first sample taken at 24 hours into the infusion. During the infusion period the exposure to AZD1152 hQPA was about 3-fold higher than that to AZD1152. Following the end of infusion the plasma concentrations of AZD1152 declined very rapidly, approaching the lower limit of quantification of the assay (0.25 ng/mL) by no later than 6 hours post the end of infusion. Plasma concentrations of AZD1152 hQPA initially declined rapidly followed by a slower bi-phasic elimination with low plasma concentrations (~1.0 ng/mL) still detectable by the time of the start of the next cycle (Day 21). The half-life of AZD1152 hQPA was about 3.5 days. About 95% of the exposure to AZD1152 hQPA was observed in the period up to 24 hours post the end of infusion. There was no accumulation of AZD1152 hQPA on repeat cycle administration.

Summary of pharmacodynamic results

Limited data for PD endpoints were available and thus no conclusions can be made. However, the cytogenetic data do indicate that clinical responses (CR, CRi or PR) were seen across all 3 Medical Research Council prognostic groups. Cytogenetic data were adverse [unfavourable] in 4 patients; intermediate in 8 patients and favourable in 1 patient (baseline

cytogenetic assessments were not available for 3 of the responding patients. Thus, some patients with poor prognostic cytogenetics responded to AZD1152 treatment.

Summary of pharmacokinetic/pharmacodynamic relationships

Limited data for PD endpoints were available and thus no conclusions on PK/PD can be made.

Summary of safety results

No safety concerns were identified, other than those currently documented in the emerging safety profile for AZD1152 (alopecia, myelotoxicity and stomatitis/mucosal inflammation). All 64 patients had at least 1 AE, which is as expected for a population of patients with AML. The majority of AEs were considered to be manageable through supportive care and/or dose modification and only a small number of patients (4 patients) discontinued AZD1152 due to AEs. The most common AEs across both phases (ie, 64 patients) were stomatitis/mucosal inflammation (34 patients), febrile neutropenia (28 patients), pyrexia (27 patients), diarrhoea (26 patients), fatigue (25 patients) and nausea (25 patients). The most commonly reported Grade 3 or 4 AEs were febrile neutropenia (23 patients) and stomatitis/mucosal inflammation (16 patients). However, most of the events reported were Grade 1 or 2.

Routine ongoing pharmacovigilance in September 2008 identified stomatitis as a potential signal. After review of the AE reports, AstraZeneca concluded that the majority of the reported events of mucositis (preferred term: mucosal inflammation) are essentially oral mucositis (ie, stomatitis) and do not relate to a general inflammation of the mucosal membranes. In this study, 34 of the 64 patients had an AE of stomatitis and/or mucosal inflammation; an additional 11 patients had other AEs that could represent stomatitis/mucosal inflammation. Analysis of the safety data also identified that diarrhoea, nausea and vomiting required further evaluation. Diarrhoea, nausea and vomiting were reported in 26, 25, and 17 patients, respectively; 3 patients had Grade 3 events (2 had diarrhoea and 1 had nausea).

Four patients had an AE with an outcome of death: sepsis and disease progression; cerebral fungal infection; Escherichia sepsis and disease progression; and 1 patient due to an unknown cause. Forty-five of the 64 patients had an SAE; 20 patients had an SAE considered by the investigator to be related to study treatment. Four patients had an AE that led to permanent discontinuation of AZD1152 (Grade 4 neutropenia; Grade 3 pulmonary mycosis; Grade 5 sepsis; Grade 3 stomatitis/mucosal inflammation); only the event of pulmonary mycosis was not considered by the investigator to be related to study treatment.

Review of the laboratory data was heavily confounded by the extent of disease under evaluation, prior treatment with chemotherapy and concurrent medications (eg, transfusions). However, other than febrile neutropenia and neutropenia, there were no consistent clinically relevant trends in other clinical laboratory parameters and myelosuppression was manageable with growth factor and blood product support. The mean time to the neutrophil nadir for Cycle 1 was approximately 9 days (range: 3 to 23 days). There was no evidence to suggest that AZD1152 was associated with cardiac arrhythmia events. Independent analysis of the electrocardiograms did not reveal any cardiac safety concerns, eg, QT interval corrected for heart rate.