AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1152
Study Code	D1531C00008
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A Phase I, Open-Label, Multi-centre Study to Assess the Safety, Tolerability, and Pharmacokinetics of AZD1152 in Japanese Patients with Acute Myeloid Leukaemia

Study dates: First patient enrolled: 20 November 2007
Last patient last visit: 4 August 2009

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

16 patients were enrolled at 8 centres in Japan.

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	**Primary**	
To assess the safety and tolerability of AZD1152 in patients with AML by assessment of AEs, vital signs, ECG parameters, clinical chemistry, haematology (including clotting parameters) and urinalysis	AEs, vital signs, ECG parameters, clinical chemistry, haematology (including clotting parameters) and urinalysis	Safety
Secondary	**Secondary**	
To determine the PK of AZD1152 hQPA (the active moiety of AZD1152, the pro-drug), and if possible AZD1152, from the observed concentration-time profiles with analysis of non-compartmental PK parameters which, depending on the data may include C_{max}, AUC, $AUC_{(0-t)}$, t_{max}, $t_{1/2}$ and CL/F and V_{ss}/F	Non-compartmental PK parameters which, depending on the data may include C_{max}, AUC, $AUC_{(0-t)}$, t_{max}, $t_{1/2}$ and CL/F and V_{ss}/F	PK
To obtain a preliminary evaluation of the role of renal excretion in the disposition of AZD1152 and AZD1152 hQPA by determination of the fraction of the dose (%) excreted in the urine and renal clearance of AZD1152 and AZD1152 hQPA at steady state	Fraction of the dose (%) excreted in urine and renal clearance of AZD1152 and AZD1152 hQPA at steady state	PK
To investigate the effect of AZD1152 on the levels of leukemic blasts in blood samples by analysis of biomarkers of inhibition of Aurora kinase activity and other biomarkers of activity	Leukemic blasts from blood were analysed for biomarkers of inhibition of Aurora kinase activity and other biomarkers of activity eg, markers of survival, proliferation and apoptosis; cellular size and cellular ploidy (DNA content)	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
To assess the effect of AZD1152 on the rate of CR, CRi, and PR in patients with AML	Rate of CR, CRi, and PR	Efficacy

AML: Acute myeloid leukaemia, AE: Adverse event, ECG: Electrocardiogram, AZD1152 hQPA: AZD1152 hydroxy quinazoline pyrazole anilide, PK: Pharmacokinetics, PD: Pharmacodynamic, CR: Complete remission, CRi: Complete remission with incomplete blood count recovery, PR: partial response

Study design

This was a multi-centre Phase I, open-label, multiple ascending dose escalation study to determine the maximum tolerated dose (MTD) and explore the safety, tolerability, pharmacokinetic and biological effect of a continuous 7-day administration of AZD1152 once every 21 days (7 days treatment followed by 14 days off treatment) in patients with AML.

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 level was determined once 3 patients had been followed for 21 days. If a dose-limiting toxicity (DLT) occurred, the cohort for that dose was expanded to a maximum of 6 evaluable patients before a decision was taken on that dose level. The MTD was the dose level at which 0 or 1 patient(s) experienced a DLT with at least 2 patients experiencing a DLT at the next higher dose level (non tolerated dose level). A minimum of 6 evaluable patients must have been treated at the MTD.

Once the MTD was established, additional patients were to be entered if required to further confirm the safety, tolerability and pharmacokinetics of this dose.

Evaluable patients were defined as those who experienced a DLT or those who received at least 80% of the total dose of AZD1152 over 7 days scheduled for Cycle 1 and whom the safety evaluation for Cycle 1 was completed.

Target subject population and sample size

The target population was patients aged over 20 years with AML, including:

- patients with relapsed or refractory AML for which no standard therapies were anticipated to result in durable 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.

This study was designed to provide adequate tolerability, safety, pharmacokinetic and pharmacodynamic data whilst exposing as few patients to the study medication and procedures as possible. This study was designed to ensure at least 6 evaluable patients were recruited at the dose deemed to be the maximum tolerated dose.

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

AZD1152 was provided as a 100 mg lyophile and supplied with 5 mL diluent for reconstitution to produce a 20 mg/mL concentrate for infusion. The required volume of

concentrate was further diluted in commercially available 0.9% sodium chloride injection prior to administration as an intravenous infusion.

The total starting dose for the 7-day continuous dosing schedule was 50 mg. Dose escalation occurred based on emerging safety data. Five batches of AZD1152 100 mg (Batch numbers: D1531C8-1, D1531C8-2, D1531C8-3, D1531C8-4, D1531C8-5E) and 5 batch of diluent (Batch number: D1531C8-1, D1531C8-2, D1531C8-3, D1531C8-4, D1531C8-5E) were used in this study.

Duration of treatment

Each patient was treated with a continuous 7-day infusion of AZD1152 given every 3 weeks or until such time that either the patient was withdrawn due to toxicity or, in the opinion of the investigator, was no longer receiving benefit from the treatment.

It was anticipated that patients received 3 cycles of treatment, although patients could continue with treatment if in the opinion of the investigator they were continuing to receive benefit. The planned schedule could change as a result of emerging safety data.

Statistical methods

No formal statistical analysis was performed. Safety, tolerability and pharmacokinetic and pharmacodynamic data were listed for each patient and summarised at each time point by nominal dose for all patients with the exception of PK which was summarised by both actual dose and nominal dose. Observed response rates were calculated for the secondary outcome variables of CR, CRi, PR and for the combined secondary outcome variable of CR+CRi and overall response (CR+CRi+PR) at the MTD.

Subject population

- A total of 16 patients were enrolled in this study and all 16 patients (5 in the 50 mg cohort, 3 in the 400 mg cohort, 5 in the 800 mg cohort, and 3 in the 1200 mg cohort) received AZD1152.

- All 16 patients discontinued from the study. Nine of the 16 patients (56.3%) discontinued due to disease progression (main reason for premature discontinuation was “condition under investigation worsened” and “lack of therapeutic response”). Four of the 16 patients (25.0%) discontinued due to death from disease progression. One of the 16 patients (6.3%) discontinued due to an serious adverse event (SAE) of CTCAE Grade 4 septic shock. One of the 16 patients (6.3%) discontinued due to safety reasons, as judged by the reporting investigator. One of the 16 patients (6.3%) discontinued due to the investigator’s decision for a “change of treatment policy”.

- There were no important protocol deviations. All 16 patients were included in each analysis set.

- Of the 16 patients who received treatment, 4 patients (25.0%) were ≤60 years of age and 12 patients (75.0%) were ≥61 years of age (5 of the 12 patients [31.3%] were ≥71 years of age). Ten of the 16 patients (62.5%) were male and the remaining 6 patients (37.5%) were female. Only patients of Japanese origin were eligible for this study.

- Most of the 16 patients (13 [81.3%] patients) had a WHO performance status of 0 or 1. Eight of the 16 patients (50.0%) had de novo AML, 5 of the 16 patients (31.3%) had AML secondary to myelodysplatic syndrome, 1 of 16 patients (6.3%) had AML secondary to myeloproliferative disorder, and 1 of 16 patients (6.3%) had AML secondary to chemotherapy. The AML type of 1 patient was listed as "Other (multilineage dysplasia)". The AML status for 3 of the 16 patients (18.8%) was newly diagnosed, 5 of the 16 patients (31.3%) were in first relapse, 2 of the 16 patients (12.5%) were in second relapse, and 1 of the 16 patients (6.3%) was in their sixth relapse. Five of the 16 patients (31.3%) had refractory disease. At screening, 14 of the 16 patients (87.5%) had a white blood cell count of ≤9.9 x 10^9/L. Fourteen patients of the 16 patients (87.5%) had received at least 1 course of chemotherapy. No patients received prior radiotherapy

Summary of efficacy results

Three responders (18.8%) have been observed in this study. Two patients in the 400 mg cohort experienced either CRi or PR during Cycle 1. A patient in the 1200 mg cohort experienced CRi after completion of Cycle 2.

Summary of pharmacokinetic results

Following 7-day infusion of AZD1152 at 50 mg, 400 mg, 800 mg and 1200 mg, plasma concentrations of AZD1152 reached a plateau by the first sampling point (24 hours after beginning of infusion) and the plateau concentration of AZD1152 hQPA was 3.3 to 4.3-fold higher than that of AZD1152.

Following the end of infusion (EOI) of AZD1152, the plasma concentrations of AZD1152 fell rapidly and were at or below the lower limit of quantification (LLOQ, 0.25 ng/mL) by no later than 24 h post-EOI with exception of a patient in the 400 mg cohort. The plasma concentrations of AZD1152 hQPA declined in a tri-phasic manner with concentrations (0.367–2.06 ng/mL) still detectable by the time of the start of the next cycle (Day 21) in all the patients at dose level of more than 400 mg. The decline of the plasma concentration was very fast at the initial phase with concentrations down to 1/3 of the concentration at steady state (C_{ss}) by 2 hours post-EOI and 1/5 of the C_{ss} by 6 hours after end of infusion. Thereafter, the decline was slower with longer $t_{½}$ at the terminal phase.

The urinary concentrations of AZD1152 were not quantifiable (below LLOQ) in all the samples, and percent of dose excreted into urine (f_e) and renal clearance (CL_R) were incalculable, suggesting little or no excretion of unchanged drug in urine.

Exposure of both AZD1152 (in terms of mean concentration at steady state: $C_{ss\ mean}$ and area under the plasma concentration-time curve from 0 to EOI: $AUC_{(0\text{-}EOI)}$) and AZD1152 hQPA (in terms of $C_{ss\ mean}$, $AUC_{(0\text{-}EOI)}$ and area under the plasma concentration-time curve from 0 to 192 h: $AUC_{(0\text{-}192\ h)}$) appeared to increase in a dose proportional manner across the dose range of 50 mg to 1200 mg studied.

Formal analysis to assess the dose-proportionality of exposure of AZD1152 and AZD1152 hQPA was performed using power model although there is limited data for this analysis and 95% confidence interval of parameter β included "1", suggesting the dose-proportionality of the exposure of AZD1152 and AZD1152 hQPA.

Plasma concentration data were obtained for Cycle 3 from only 3 patients (1 each in the 50 mg, 400 mg and 1200 mg cohorts). There was observed no marked time dependency from these limited data.

Summary of pharmacodynamic results

There were no consistent clear trends in the biomarker results.

Summary of pharmacokinetic/pharmacodynamic relationships

Limited data were available on a small number of patients, thus PK/PD analysis for the relationship with plasma exposure (AZD1152 hQPA) was performed using a graphical approach only. There were no consistent clear trends in the PK/PD relationship.

Summary of safety results

- There were no safety concerns identified from the safety data reported in this study, other than those currently documented in the emerging safety profile for AZD1152 (myelotoxicity, alopecia and stomatitis/mucositis).

- The most common AEs (≥5 patients) were febrile neutropenia (10 of 16 patients [62.5%]), neutropenia (9 of 16 patients [56.3%]), leukopenia (8 of 16 patients [50.0%]), thrombocytopenia (7 of 16 patients [43.8%]), and fatigue (6 of 16 patients [37.5%]).

- The most commonly reported CTCAE Grade 3 or 4 AEs (≥5 patients) were febrile neutropenia (10 of 16 patients [62.5%]), neutropenia (9 of 16 patients [56.3%]), leukopenia (7 of 16 patients [43.8%]), and thrombocytopenia (7 of 16 patients [43.8%]). Most of these events were considered by the reporting investigator to be related to study treatment.

- One of the 16 patients (6.3%) discontinued treatment and died due to a SAE of CTCAE Grade 4 septic shock; the event was not considered by the reporting investigator to be related to study treatment.

- Six of the 16 patients (37.5%) had a total of 10 events that were considered other significant adverse events (OAE).

- There were no consistent clinically relevant trends other than cytopenia including neutropenia in the laboratory data.

- There were no consistent clinically relevant trends in the vital signs and ECGs.

- No DLTs were reported in this study. An MTD was not reached. Dose escalations were continued to 1200 mg to assess safety. However, it was not considered appropriate to escalate AZD1152 dosing above 1200 mg, which could be non-tolerated, based on data from Western patients.