AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1152
Study Code	D1531C00018
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A Phase I, open-label, multi-centre, multiple ascending dose study to assess the safety and tolerability of AZD1152 in combination with low dose cytosine arabinoside (LDAC) in patients with acute myeloid leukaemia (AML)

Study dates:	First subject enrolled: 12 June 2009 Last subject enrolled: 30 June 2010
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)

Two sites in the United States of America and 2 sites in France.

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 evaluate the safety and tolerability, and determine a recommended Phase II dose of AZD1152 in combination with LDAC	AEs, vital signs, ECGs, clinical chemistry, haematology (including clotting parameters) and urinalysis	Safety
Secondary	**Secondary**	
To determine the PK of AZD1152, AZD1152 hQPA and LDAC when AZD1152 is given in combination with LDAC, and to compare to their PK when given alone	**Key:** AZD1152: C_{ss} and $AUC_{(0-t)}$ AZD1152 hQPA: C_{ss} and AUC LDAC: C_{max} and AUC **Other:** AZD1152 hQPA: $AUC_{(0-t)}$, $t_{1/2}$, CL, V_{ss}, V_z and λ_z LDAC: $AUC_{(0-t)}$, t_{max}, $t_{1/2}$, CL, V_{ss}, V_z and λ_z	PK
Exploratory	**Exploratory**	Efficacy
To make a preliminary assessment of efficacy of AZD1152 combined with LDAC	The proportion of patients achieving CR, CRi or PR, as evaluated by the Investigator	

AE Adverse event; 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; CL Total body clearance of drug from plasma; C_{max} Maximum plasma (peak) drug concentration; CR Complete remission; CRi Complete remission with incomplete recovery of neutrophils and/or platelets; C_{ss} Steady-state drug concentration in plasma during constant rate infusion; ECG Electrocardiogram; hQPA Hydroxy-quinazoline pyrazole anilide; LDAC Low dose cytosine arabinoside; PK Pharmacokinetic(s); PR Partial remission; $t_{1/2}$ Terminal elimination half-life; t_{max} Time to reach peak or maximum concentration; V_{ss} The apparent volume of distribution at steady-state; V_z The apparent volume of distribution during terminal (λ_z) phase; λ_z Slowest disposition rate constant.
Note: There was 1 other exploratory objective (pharmacogenetics); no data are presented for this objective in the clinical study report.

Study design

This was a Phase I, open label, multicentre, non-randomised multiple ascending dose study to assess the safety, tolerability and pharmacokinetic(s) (PK) of AZD1152 in combination with low dose cytosine arabinoside (LDAC), and to establish a recommended dose of AZD1152 when combined with LDAC.

The starting dose of AZD1152 was 800 mg, in combination with LDAC 400 mg (LDAC 20 mg given twice daily for 10 days = total 400 mg). The dose of AZD1152 was not to be increased above 1200 mg or lowered below 400 mg; the dose of LDAC was to remain at 400 mg.

In the dose escalation part of the study, cohorts of patients received escalating doses of AZD1152 (starting at 800 mg) until the non-tolerated combination dose was reached. In each cohort, the first 3 patients recruited to that cohort completed the first 28-day cycle of treatment and were assessed. If fewer than 2 of 3 patients had a dose limiting toxicity (DLT) in Cycle 1, an additional 3 patients were dosed in that cohort. If 2 or more patients had a DLT, no further patients were recruited at that dose.

If 0 or 1 patient from the cohort of 6 had a DLT the AZD1152 dose in the combination could be increased, if the Safety Monitoring Committee (SMC) considered this appropriate. If 2 or more patients in a cohort had DLTs, no more patients were enrolled to that cohort and the dose was not to be increased. The SMC was responsible for identifying the recommended Phase II combination dose following evaluation of all the available safety data. The recommended combination dose was to include the highest dose of AZD1152 with which there were less than 2/6 DLTs during Cycle 1 in the dose escalation phase. The recommended combination dose could have been lower than the maximum tolerated combination dose, eg, if data beyond Cycle 1 suggested poorer longer term tolerability.

Following the preliminary recommendation of a Phase II combination dose, an expansion cohort of patients were enrolled until 12 evaluable patients (including those in the original dose escalation cohort) had received AZD1152 in combination with LDAC at the recommended dose.

Target subject population and sample size

The study included male or female patients aged ≥60 years with newly diagnosed acute myeloid leukaemia (AML), who were considered unsuitable to receive intensive induction chemotherapy regimens, for example, due to poor performance status, age or co-morbid conditions.

The number of patients was based on the desire to obtain adequate safety and tolerability data, whilst exposing as few patients as possible to the study treatment and procedures. Approximately 18 patients were planned to be recruited.

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

Table S2 Details of investigational product and other study treatments

Investigational product	Dosage form, strength and route of administration	Manufacturer	Formulation number	Batch number
AZD1152	Lyophile, 100 mg, 7-day intravenous infusion	AstraZeneca	F13353	70677B09, 72470H09, S09H01
	Diluent, 5 mL, 7-day intravenous infusion	AstraZeneca	F13412	60968F08, 72408A09

Commercially marketed LDAC was centrally sourced by AstraZeneca.

Duration of treatment

AZD1152 was to be dosed as a 7-day continuous intravenous infusion throughout the study. LDAC was to be administered as a 20 mg subcutaneous injection given twice daily for 10 days throughout the study (total 400 mg); the dose of LDAC was not to be increased. AZD1152 and LDAC were to be administered on a 28-day cycle (ie, AZD1152 on Day 1 through Day 7 and LDAC on Day 1 through Day 10, followed by an 18-day break from treatment prior to the next 28-day cycle starting).

It was anticipated patients would receive at least 3 cycles of treatment unless deemed inappropriate by the Investigator. Further cycles of combination therapy could be given if the Investigator considered the patient was still deriving benefit.

Statistical methods

No formal statistical hypothesis testing was performed. All data were summarised descriptively including tables, listings and graphs, as appropriate.

Subject population

The first patient was enrolled in the study on 12 June 2009 and the last patient was enrolled on 30 June 2010. In total, 22 patients entered the study and received treatment; 6 in the AZD1152 800 mg + LDAC 400 mg group; 13 in the AZD1152 1000 mg + LDAC 400 mg group and 3 in the AZD1152 1200 mg + LDAC 400 mg group. Dose escalation information is provided in Table S3.

Table S3 Dose escalation

Combination dose (n=patients)	
AZD1152 800 mg + LDAC 400 mg (n=6)	One of 6 patients had a CTCAE Grade 3 SAE (pancytopenia) considered by the reporting Investigator to be related to AZD1152 and LDAC. However, the Investigator considered the tolerability of AZD1152 in combination with LDAC to be acceptable and this event was not considered a DLT. The SMC provided a unanimous recommendation to escalate the dose of AZD1152 to 1200 mg with LDAC to remain at 400 mg.
AZD1152 1200 mg + LDAC 400 mg (n=3)	Two of 3 patients developed CTCAE Grade 3 stomatitis/mucositis (1 SAE and 1 AE); both were considered DLTs. The SMC decided that Cohort 2 should not continue and to explore an intermediate combination dose of AZD1152 1000 mg and LDAC 400 mg.
AZD1152 1000 mg + LDAC 400 mg (n=13)	Seven patients were entered into the dose escalation phase of Cohort 3. One of the first 3 patients died of causes unknown on Day 12 of Cycle 1. The patient was found dead by hospital staff and after further queries to the site no cause of death was identified; no autopsy was performed. (The Investigator did not consider the event a DLT.) An additional 4 patients were recruited to ensure a fully evaluable cohort during the dose escalation phase. None of the AEs or SAEs reported in Cohort 3 were considered to be DLTs. Consensus approval was given by the SMC to designate AZD1152 1000 mg with LDAC 400 mg as the maximum tolerated combination dose. A further 6 patients were recruited to the expansion phase of the AZD1152 1000 mg + LDAC 400 mg cohort to give a total of 13 patients.

AE Adverse event; CTCAE Common terminology criteria for adverse events; DLT Dose limiting toxicity; LDAC Low dose cytosine arabinoside; SAE Serious adverse event; SMC Safety monitoring committee.

Twenty of the 22 patients have discontinued the study; 2 patients were ongoing at data cut-off (17 December 2010). Of the 20 patients who discontinued the study (6 in the AZD1152 800 mg + LDAC 400 mg group, 11 in the AZD1152 1000 mg + LDAC 400 mg group and 3 in the AZD1152 1200 mg + LDAC 400 mg group), most discontinued due to condition under investigation worsened or lack of therapeutic response (14 of 22 patients). Two patients withdrew from the study due to adverse events (AEs) (sudden death and hypoxia); neither event was considered by the reporting Investigator to be related to treatment and both patients died on the same day as withdrawal from the study was reported.

The mean age of patients was 71.1 years, and the majority of patients were male (14 patients) and White (21 patients). In total, 9 (40.9%) patients had AML secondary to myelodysplastic syndrome, 8 (36.4%) patients had de novo AML, 2 (9.1%) patients had AML secondary to myeloproliferative disorder, 2 (9.1%) patients had an “other” type of AML (both were chronic myelomonocytic leukaemia) and 1 (4.5%) patient had AML secondary to chemotherapy. Sixteen of the 22 patients had data for bone marrow chromosomal aberrations, all 16 had cytogenetics considered intermediate (intermediate no abnormality [9 patients], intermediate del (7q) [4 patients], intermediate other numerical [2 patients] or intermediate +8 [1 patient]).

Summary of efficacy results

As raw data pertaining to the response rate criteria were not collected, it was not possible to programmatically derive an assessment of response; therefore, the response rate presented is based on the Investigators assessments of response. Ten of the 22 patients (45.5%) had a response (complete response [CR], complete remission with incomplete recovery of neutrophils and/or platelets [CRi] or partial remission [PR]). Eight of the 22 had a CR or CRi (rate: 36.4%; 80% confidence interval [CI]: 24.6, 50.0).

- In the AZD1152 800 mg + LDAC 400 mg group, 2 CRs and 1 PR were reported out of the 6 patients (CR+CRi rate: 33.3%; 80% CI: 14.8, 59.1).
- In the AZD1152 1000 mg + LDAC 400 mg group, 6 responses were observed out of the 13 patients (3 CR, 2 CRi and 1 PR) (CR+CRi rate: 38.5%; 80% CI: 23.4, 56.1).
- In the AZD1152 1200 mg + LDAC 400 mg group, 1 CR was reported out of the 3 patients (CR+CRi rate: 33.3%; 80% CI: 7.4, 67.9).

Six of the responders had their best response after 1 cycle, 2 after 2 cycles and 2 after 3 or more cycles of AZD1152 + LDAC.

Summary of pharmacokinetic results

The PK profiles of AZD1152 and AZD1152 hydroxy-quinazoline pyrazole anilide (hQPA) were similar to those seen previously. Steady-state concentrations for AZD1152 and AZD1152 hQPA were seen from 24 hours after the start of infusion and were maintained until the end of the infusion. Levels of AZD1152 disappeared rapidly and were usually not detectable 2 hours after the infusion was stopped. AZD1152 hQPA was eliminated in a biphasic manner after the end of infusion, with an initial rapid decline followed by a longer terminal phase with a terminal elimination half-life of 3.5 to 4.5 days. LDAC was rapidly absorbed with maximum plasma (peak) drug concentration generally observed up to 1 hour after administration. LDAC was rapidly eliminated in a mono-phasic manner with a terminal elimination half-life between 1 and 2 hours. Exposure to LDAC was similar on Day 7 and Day 10 indicating no evidence of an effect of AZD1152 on the PK of LDAC, irrespective of the AZD1152 dose administered.

Summary of safety results

No safety concerns were identified, other than those currently documented in the emerging safety profile for AZD1152 (alopecia, diarrhoea, myelotoxicity, nausea, stomatitis/mucositis and vomiting).

All 22 patients in the study had at least 1 AE, which is expected for a population of patients with AML. The majority of AEs were considered to be manageable through supportive care and/or dose modification. The most common AEs across all 3 cohorts were febrile neutropenia (59.1%), nausea (50.0%), diarrhoea (45.5%), oedema peripheral (40.9%) and

stomatitis (40.9%). The most commonly reported common terminology criteria for adverse events (CTCAE) Grade 3 or higher AE was febrile neutropenia (59.1%). Most patients had an AE of infection and 7 (31.8%) patients had an AE of infection of CTCAE Grade 3. Overall, pneumonia was the most common AE of infection reported (3 patients at Grade 3).

Three patients had an outcome of death during the study: disease progression; hypoxia (AE) and disease progression; and sudden death (AE; unknown cause). Neither AE was considered by the reporting Investigator to be related to AZD1152 or LDAC. Fifteen of the 22 patients in all 3 cohorts had a serious adverse event (SAE); 5 patients had an SAE considered by the reporting Investigator to be related to AZD1152 or LDAC. One patient discontinued the study due to an AE (hypoxia), the patient died the same day; the event was not considered by the reporting Investigator to be related to study treatment.

The principal expected adverse drug reactions seen to date with AZD1152, across a range of different tumour types, doses and dose regimens, are alopecia, diarrhoea, myelotoxicity (in particular neutropenia, febrile neutropenia and leucopenia), nausea, stomatitis/mucositis and vomiting. In this study, 12 of the 22 patients had an AE of stomatitis/mucositis (grouped terms) and 14 of the 22 patients had an AE of febrile neutropenia (grouped terms). Alopecia, diarrhoea, nausea and vomiting were reported by 6, 10, 11 and 6 of the 22 patients, respectively.

Haemoglobin was generally well maintained during treatment with AZD1152, but all patients had profound falls in platelets and neutrophils and also lymphocytes, and consequently, total leucocyte counts. However, the review of the laboratory data in this patient population is heavily confounded by the extent of disease under evaluation, previous treatment with chemotherapy and concurrent medications (eg, transfusion). Other than febrile neutropenia, neutropenia and thrombocytopenia (the latter is an acknowledged adverse reaction with cytosine arabinoside), there were no consistent clinically relevant trends in other clinical laboratory parameters, and myelosuppression was manageable with growth factor and blood product support.

There were no clinically relevant treatment-related changes or trends in blood pressure or pulse rate, in patients exposed to the AZD1152 and LDAC combination during the study. In general, the cardiac safety profile was consistent with an elderly population with AML.