AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1152
Study Code	D1531C00012
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A Phase I, Open, Non-randomised, Single-centre Study to Assess the Metabolism, Excretion and Pharmacokinetics of AZD1152 and AZD1152 hQPA Following Intravenous Administration of [^{14}C]-AZD1152 in Patients With Acute Myeloid Leukaemia (AML)

Study dates: First patient enrolled: 05 November 2009
Data cut-off date used for analysis: 20 August 2010

Phase of development: Clinical pharmacology (I)

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

The study was conducted at 1 centre in the United Kingdom.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Primary Objectives	Outcome variables
The primary objective of the study was to assess the metabolism, excretion and pharmacokinetics of AZD1152 and AZD1152 hydroxyl-quinazoline pyrazole anilide (hQPA) following an intravenous (iv) infusion of AZD1152 and a short infusion of [^{14}C]-AZD1152 to patients with acute myeloid leukaemia (AML).	– The concentration of total radioactivity, AZD1152 and AZD1152 hQPA in plasma and their ratios – The concentration of total radioactivity in blood and its blood/plasma concentration ratios – The derived plasma pharmacokinetic parameters for AZD1152 and AZD1152 hQPA (area under the curve from time zero to infinity, area under the plasma concentration time curve from time zero to time t, steady state drug concentration in plasma during constant rate infusion, total body clearance of drug from plasma [CL], volume of distribution (apparent) at steady state , volume of distribution (apparent) during terminal phase [V_z] and terminal elimination half-life [$t_{½}$]) – The derived urinary pharmacokinetic parameters for AZD1152 and AZD1152 hQPA (cumulative amount of each excreted in urine, fraction of each excreted into urine [fe], renal clearance of each from plasma [CL_R]) – The percentage of the [^{14}C]-AZD1152 dose recovered in urine, faeces and vomit (if presented), and the percentage of radioactive dose recovered overall – Metabolic profiles in plasma and excreta were defined. Where possible, the identity of metabolites was determined.[a]

[a] Results of the metabolite profiles are reported separately from this clinical study report (CSR).

Secondary objective	Outcome variables
To further evaluate the safety and tolerability of AZD1152 by assessments of adverse events (AEs), laboratory findings and vital signs.	– Adverse eventss, serious adverse events (SAEs) and deaths – Discontinuations for tolerability reasons – Vital signs (temperature, blood pressure, pulse rate and respiratory rate) – Electrocardiogram (ECG) parameters – Clinical chemistry, haematology (including clotting parameters) and urinalysis. – Physical examination.
To provide further information on the efficacy of AZD1152 by measurement of individual patient response, as evaluated by the Investigator.	– Investigator assessment of response (complete remission [CR], complete remission with incomplete recovery of neutrophils and platelets, partial remission, or non-response).

Exploratory objectives[a]	Outcome variables
To collect and store DNA, derived from a saliva sample, for potential exploratory research into genes that may influence the response to AZD1152 and/or development of AML. Genes that may have been analysed included, but were not limited to, absorption, distribution, metabolism and excretion-related genes, MDR1, MRP1, fms-related tyrosine kinase 3, p53, p51 and aurora kinase B. To collect cytogenetic data obtained from a diagnostic bone marrow or peripheral blood specimen for exploratory research into potential correlations of cytogenetic status with response.	– Correlation of polymorphisms with variation in pharmacokinetic, pharmacodynamic, safety or response parameters observed in patients treated with AZD1152. Correlation of polymorphisms with occurrence and/or disease progression of AML. – Correlation of cytogenetic status with occurrence and/or disease progression of AML. Correlation of cytogenetic status to response.

[a] Results from the genetic research are reported separately from this CSR.

Study design

This was a Phase I, open-label, single-arm, single-centre, non-randomised, study in patients with AML designed to assess the metabolism, excretion, and pharmacokinetics of AZD1152 and AZD1152 hQPA following the iv administration of AZD1152 and a short infusion of [^{14}C]-AZD1152.

Target subject population and sample size

It was planned to recruit up to 6 evaluable AML patients (males or females in no particular ratio) in this study. Six patients were entered in the study and 1 patient died prior to study medication administration. Patients had relapsed or refractory AML for which no standard

therapies were anticipated to result in durable remission, or patients had newly diagnosed AML and were not considered to be suitable for standard induction and consolidation chemotherapy for medical, social or psychological reasons. The sample size was based on previous experience with mass balance studies which had found that 6 patients were sufficient to adequately characterise the rates and routes of excretion of ^{14}C-labelled compounds.

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

Patients received 1200 mg AZD1152 as an iv infusion. Non-radiolabelled AZD1152 was administered as a continuous iv infusion on Day 1 to Day 8 (168 hours) and was replaced with a 2 hour infusion of [^{14}C]-AZD1152 on Day 2 of Cycle 1 only. AZD1152 was manufactured by AstraZeneca.

The batch numbers were 09-006414AZ and 10-000426AZ for [^{14}C]-AZD1152, 70677B09 and 72722G09 for AZD1152, and 71554F09 for the diluent.

Duration of treatment

Cycle 1 was to last 28 days. Following the first treatment cycle, patients were allowed to receive subsequent continuous 7-day infusions of 1200 mg AZD1152 every 4 weeks or until such time that either the patient was withdrawn due to an AE, withdrew consent, or, in the opinion of the Investigator, the patient was no longer receiving benefit from the treatment.

Statistical methods

No formal statistical analyses were performed.

For radioactive samples (blood, plasma and excreta), data were summarised by: n, geometric mean, geometric mean + standard deviation (SD), geometric mean – SD, coefficient of variation, mean, SD, median, minimum, and maximum.

In the pharmacokinetic analyses, plasma concentration data were summarised by: n, geometric mean, geometric mean +SD, geometric mean –SD, coefficient of variation, mean, SD, median, minimum, and maximum. With the exception highlighted, the derived plasma and urine pharmacokinetic parameters were summarised by: n, geometric mean, coefficient of variation, mean, SD, median, minimum, and maximum. The exception was fe, which was summarised by: n, mean, SD, minimum and maximum.

Summary statistics and percentage counts were presented for selected demographic and baseline patient characteristics, and AE data including SAEs, deaths, and AEs of special interest.

Subject population

Six patients entered the study and 5 patients received study medication. One patient died prior to receiving study medication. Four patients completed the study and 1 patient was ongoing at the time of data cut-off as it was considered by the Investigator that this patient was still

receiving clinical benefit from the study medication. The demographic and baseline patient characteristics were representative of the intended patient population.

Summary of efficacy results

The Investigator's assessment of tumour response was available for 4 patients, of which 3 patients had non-response, and 1 patient achieved CR during Cycle 3.

Summary of pharmacokinetic results

- Following a 7-day infusion of AZD1152 1200 mg to patients with AML, AZD1152 hQPA was extensively distributed to the tissues (mean V_z 2805 L), although the rate of CL was relatively slow (mean CL 31.4 L/h). The disposition of AZD1152 was tri-phasic, with a terminal phase having a mean $t_{½}$ of 66.3 hours.

- The ratio of radioactivity in plasma to whole blood was approximately 0.7, indicating that a larger proportion of the drug-related radioactivity was associated with the plasma fraction than with the cellular components of the blood.

- The cumulative amount of AZD1152 hQPA in urine was 96.9 mg and the fraction of AZD1152 hQPA excreted was 8.1%. The CL_R for AZD1152 hQPA from plasma was 2.85 L/h. The CL_R values for AZD1152 hQPA (between 4 and 15% of the total CL of AZD1152 hQPA from plasma), indicated that the majority of CL of AZD1152 hQPA occurred via a non-renal route (ie hepatic).

- The mean total recovery was 77.3%. The major route of elimination was via faeces (50.8% of the recovered radioactivity). Renal excretion accounted for 26.6% of the recovered radioactivity. The recovery of radioactivity was generally slow, with the majority of radioactivity (>67%) recovered by 120 hours. In 2 patients, however, the majority of radioactivity was recovered in the last 2 collection periods, and it was evident that radioactivity was still being eliminated beyond the end of the 192 hour collection period.

Summary of pharmacogenetic results

Pharmacogenetic results are reported separately from this CSR.

Summary of safety results

Five patients received Cycle 1 as per protocol and therefore received the [^{14}C]-AZD1152 iv solution 1.05 mg/mL for 2 hours during Cycle 1 in addition to non-radiolabeled AZD1152 1200 mg. Three patients went on to receive further treatment cycles, all after delays from the protocol-scheduled cycle times; 1 patient received Cycle 2 only, 1 patient received Cycle 2 and started Cycle 3 but stopped treatment on the same day, and 1 patient received Cycles 2 and 3. After completing Cycle 3, the patient remained in the study as the Investigator considered the patient was receiving clinical benefit from study medication.

As would be expected in this patient population, a relatively large number of AEs was reported during the study. All 5 patients in the Safety Set experienced an AE, with 91 events reported for these patients in total. The most frequently reported AEs during the study were nausea, stomatitis, hypocalcaemia, vomiting, febrile neutropenia and alopecia. The occurrence of the AEs of special interest was as expected with use of AZD1152. Three patients experienced an SAE and 1 patient had an AE with an outcome of death since starting treatment and up to 28 days following the last administration of study medication. Three patients had an AE of National Cancer Institute common terminology criteria for adverse events (NCI CTCAE) grade 3 or higher and 1 patient withdrew from the study due to an AE. Of the 3 patients who experienced AEs of NCI CTCAE AE grade 3 or above, all 3 patients experienced grade 3 AEs, 1 patient experienced grade 4 AEs and 1 patient experienced a grade 5 AE (outcome = death).

In total, 3 patients died: 1 patient had an AE of mulit-organ failure with an outcome of death during the reporting period ie during treatment or up to 28 days after the end of treatment, 1 patient died due to neutropenic sepsis during screening before study medication administration, and 1 patient died due to the disease under investigation more than 28 days after the last dose of study medication.

Although some abnormalities were seen for laboratory, vital signs, ECG and physical examination data, they were considered to be consistent with the patients' underlying disease.