Clinical Study Report Synopsis

Drug Substance	AZD1208
Study Code	D4510C00001
Edition Number	1
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A Phase Ia/Ib, Open-Label, Multicentre, Two-Part Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of AZD1208 Administered Daily in Adult Patients with Recurrent or Refractory Acute Myelogenous Leukemia (AML)

Study dates:	First patient enrolled: 10 February 2012
	Last patient last visit: 13 May 2014
Phase of development:	Phase 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 centres

The study was conducted at 4 study centers in 2 countries (USA and Canada).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary objectives and the outcome variables are presented in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary			
Part A	Safety	To identify an MTD of AZD1208 on a daily schedule by assessment of incidence of DLTs	Incidence of DLTs
Part B	Efficacy	To assess the effect of AZD1208 on the rate of CR including CRi in FLT3 mutation positive and FLT3 wild-type (FLT3 mutation negative) patients with first or second relapsed or refractory AML, with CR and CRi defined by bone marrow and blood myeloblast counts and recovery of normal hematopoiesis	Rate of CR including CRi in FLT3 mutant patients
Secondary			
Part A	Safety	To evaluate the safety and tolerability of AZD1208 on a daily schedule by assessment of CTCAE grade and type of an AE, and changes in laboratory values and vital signs	Assessment of CTCAE grade and type of an AE, Changes in laboratory values, Changes in vital signs
	PK	To characterize the PK of AZD1208 in patients for a daily schedule	Single dose part (or first dose): C_{max}, t_{max}, λ_z, AUC_{0-24} AUC_{0-t}, AUC, MRT, CL/F, V_z/F, CL_R, $t_{½}\lambda z$ and Ae; % dose Multiple dose part: $C_{ss,max}$, $C_{ss,min}$, $C_{ss,avg}$, $t_{ss,max}$, AUC_{ss}, CL_{ss}/F, $V_{ss,Z}$/F, $R_{AC(AUC)}$, $R_{AC(Cmax)}$), CLR_{ss}, $Ae_{,ss}$, and $fe_{,ss}$, % dose

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	Efficacy	To seek preliminary evidence of the anti-leukemic activity of AZD1208 via the effect on rate of CR, CRc, CRm, CRi, PR, and overall response (MLF, CR, CRi, PR).	Rate of CR, CRc, CRm, CRi, PR according to the modified Cheson Criteria and overall response (CR, CRi, MLF, PR)
Part B	Safety	To evaluate the safety and tolerability of AZD1208 on a daily schedule by assessment of CTCAE grade and type of an AE, and changes in laboratory values and vital signs	Assessment of CTCAE grade and type of an AE, Changes in laboratory values, Changes in vital signs
	PK	To characterize the PK of AZD1208 in patients for a daily schedule	Single dose part (or first dose): Cmax, tmax, λ_z, AUC_{0-24}, AUC_{0-t}, AUC, MRT, CL/F, V_z/F, CL_R, $t_{½}\lambda z$ and Ae; % dose Multiple dose part $C_{ss,max}$, $C_{ss,min}$, $C_{ss,avg}$, $t_{ss,max}$, AUC_{ss}, CL_{ss}/F, $V_{ss,Z}$/F, $R_{AC(AUC)}$), $R_{AC(Cmax)}$), CLR_{ss}, $Ae_{,ss}$, and $fe_{,ss}$, % dose
	Efficacy	To assess the effect of AZD1208 on rate of CR, CRc , CRm, CRi, PR, and overall response (MLF, CR, CRi, PR)	Rate of CR, CRc, CRm, CRi, PR according to the modified Cheson Criteria and overall response (CR, CRi, MLF, PR)
	Efficacy	To assess the effect of AZD1208 on duration of CR or CRi based on time from first documentation of CR to relapse, as defined by reappearance of leukemic blasts in blood or bone marrow, recurrence of previously documented cytogenetic abnormality or molecular abnormality, the reappearance of new dysplastic changes, or the reappearance or development of extramedullary leukemia	Duration of response (Time from first documentation of either CR or CRi to relapse after completion of treatment)

Abbreviations: λ_z, terminal rate constant; Ae, amount of drug excreted unchanged in urine; $A_{e,ss}$, amount of drug excreted unchanged at steady state; AE, adverse event; AML, acute myelogenous leukemia; AUC, area under plasma concentration-time curve; AUC_{0-24}, area under the plasma concentration-time curve from 0 to 24 hours; $AUC_{0\,t}$, area under the plasma concentration-time curve from zero to time t [amount time/volume]; AUC_{ss}, area under the plasma concentration-time curve from zero to the end of the dosing interval; CL/F, apparent plasma clearance; CL_R, renal clearance; CL_{ss}/F, apparent plasma clearance at steady state; C_{max}, maximum plasma concentration; CR, complete remission; CRc, cytogenetic complete remission; CRi, complete remission with incomplete blood count recovery; CRm, molecular complete remission; CSP, Clinical Study Protocol; $C_{ss,avg}$, average plasma concentration at steady state; $C_{ss,min}$, minimum plasma concentration at steady state; $C_{ss,max}$, maximum plasma concentration at steady state; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; Fe, fraction of drug excreted unchanged in urine; FLT3, Fms-Like Tyrosine kinase 3; MLF, morphologic leukemia-free; MRT, mean residence time;

MTD, maximum tolerated dose; PK, pharmacokinetics; PR, partial response; $R_{AC(AUC)}$, extent of accumulation on multiple dosing based on AUC; $R_{AC(Cmax)}$, extent of accumulation on multiple dosing based on C_{max}; $t_{½}\lambda z$, terminal half-life; t_{max}, time to reach maximum concentration; $t_{ss,max}$, time to maximum plasma concentration at steady state; V_z/F, apparent volume of distribution; $V_{ss,Z}/F$, apparent volume of distribution at steady state.

Study design

This was a Phase Ia/Ib, open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of AZD1208 administered orally once daily in adult patients with relapsed or refractory acute myelogenous leukemia (AML). In addition, the pharmacodynamics of AZD1208 and any potential predictive biomarkers of anti-leukemic activity were explored. The study design allowed an escalation of dose with intensive safety monitoring to ensure the safety of the patients.

There were 2 parts planned to this study: Part A (dose escalation) and Part B (dose expansion). In Part A, the maximum tolerated dose (MTD) of AZD1208 at continual 28-day treatment cycles was decided. The MTD was defined as the highest dose at which ≥33% of at least 6 evaluable patients experienced a dose-limiting toxicity (DLT).

In Part B, the objective was to assess the efficacy of AZD1208 when administered daily for continual 28-day treatment cycles and further characterize the safety, tolerability, PK and pharmacodynamic (PD) effects. However, Part B was not performed as described in the Clinical Study Protocol due to early termination of the study.

Target subject population and sample size

Part A: Male and female patients aged 18 years and above, with relapsed or refractory AML (including AML secondary to myelodysplastic syndromes, myeloproliferative neoplasm, or chronic myelogenous leukemia) were included in the study. Approximately 30 evaluable patients were planned to be enrolled in Part A of this study. A total of 55 patients were enrolled in Part A of the study and 32 of these patients were assigned to treatment.

Part B: AML patients with Fms-Like Tyrosine kinase 3 (FLT3) mutations and no more than 2 prior salvage regimens were included. Following a Simon Minimax 2-stage design, up to 22 evaluable patients were planned to be enrolled in Part B of this study. Part B was not performed.

Investigational product and comparators: dosage, mode of administration and batch numbers

Three different doses of AZD1208 in the form of capsules were provided by AstraZeneca: 10 mg, 60 mg, and 100 mg (batch numbers 11-002555AZ/11-002246AZ, 12-000088AZ/11-002805AZ, 12-002214AZ/11-002805AZ, 12-002387AZ/11-002805AZ, 12-003087AZ/12-003068AZ, 12-003099AZ/12-002191AZ, 13-000222AZ/13-000176AZ, 13-001424AZ/ 13-001278AZ, and 13-001793AZ/13-001467AZ). AZD1208 was administered orally on a daily basis.

Duration of treatment

Patients could continue to receive AZD1208 as long as they were continuing to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria.

Statistical methods

No hypothesis testing was carried out in this study and no formal statistical comparisons were made.

A summary of dose decisions and DLTs during the first 28 days of Cycle 1 relative to the first administration of AZD1208 at those dose levels was produced. This summary included all dosed patients, and showed the number of evaluable patients at each dose level, the number of evaluable patients with DLTs, and descriptions of the DLTs. All laboratory variables of Common Terminology Criteria for Adverse Events (CTCAE) grade 4 were calculated and summarized using frequency counts and percentages in the form of shifts from baseline to maximum grade post baseline.

Efficacy was described by the investigator's assessment of the clinical response of AML. The analyses of response rates were based on the exact binomial distribution.

Summary statistics were provided for the plasma and urine concentration of AZD1208 versus nominal time and all derived pharmacokinetic parameters by dose level and day (Day 1 and Day 14).

Subject population

In Part A, a total of 55 patients were enrolled into the study at 4 study centers in 2 countries; 32 of these patients were assigned to treatment, all of whom received at least 1 dose of AZD1208 (4 received AZD1208 120 mg, 6 received AZD1208 240 mg, 6 received AZD1208 480 mg, 7 received 700 mg, and 9 received 900 mg). The most common reason for discontinuation of AZD1208 was lack of therapeutic response (19 [59.4%] patients). Other reasons included adverse events (7 [21.9%] patients) and subject decision (5 [15.6%] patients).

The mean age was 62.7 years and 26 (81.3%) patients were White. The majority of patients were male (21 [65.6%] males and 11 [34.4%] females) and the sex ratio was not balanced among dose cohorts.

Summary of efficacy results

No AML responses to monotherapy treatment, as assessed by Cheson criteria or the investigator, were observed in this study. The most common reason for patients not responding was treatment failure due to resistant disease.

Summary of pharmacokinetic results

After a single dose of AZD1208, the absorption was rapid and prolonged with a median time to reach maximum plasma concentration (t_{max}) of ~3 hours (range 1.7 hours to 23.8 hours).

The concentrations remained high until 24 hours, suggesting slow elimination of AZD1208 after a single dose. With plasma sample collection only up to 24 hours after the single dose, the elimination phase could not be clearly defined and, hence, only limited pharmacokinetic parameters could be determined. Variability was moderate across dose cohorts with higher doses leading to more variable absorption. Both maximum plasma concentration (C_{max}) and area under plasma concentration-time curve from 0 to time t (AUC_{0-t}) increased in proportion to dose after single dose across all dose cohorts. Renal clearance (CL_R) was similar across dose cohorts; <1% of the administered dose was eliminated unchanged in urine within 24 hours.

After multiple doses of AZD1208, absorption was rapid but highly variable (coefficient of variation of 70% to 120% for C_{max} and area under the plasma concentration-time curve from 0 to the time of next dosing [AUC_{tau}]). Up to 10 fold differences in concentrations were reported among patients receiving the same dose. Apparent plasma clearance increased with increasing doses which led to increases in exposure with increasing doses at steady state. Both AUC_{tau} and C_{max} generally decreased with increasing doses and this trend was most apparent in the AZD1208 700 mg and 900 mg dose cohorts. The accumulation ratio indicated that the exposure was significantly lower at steady state compared to single dose of AZD1208 for many subjects although there were several subjects who showed significant accumulation leading to highly variable exposure.

The pharmacokinetic profiles for patients with DLTs were in the same range as those seen in patients who did not have a DLT. Plasma protein binding (%free) levels of AZD1208 on Day 1 and Day 14 were similar for patients who had accumulation and no accumulation, confirming that the change in exposure to was due to change in apparent clearance and not due to changes in free fraction. The apparent reason for time-dependent PK of AZD1208 could not be determined from this study.

Summary of pharmacodynamic results

Treatment with AZD1208 resulted in a reduction in the levels of phosphorylated Bcl-2 antagonist of cell death (BAD) at serine 112 (pBAD, S112) at all dose levels tested and was consistent with inhibition of Proviral Integration Moloney virus (PIM)-1 kinase. The largest reductions in the levels of eukaryotic translation initiation factor 4E binding protein 1 (4EBP1) at serine 65 (p-4EBP1, S65) were seen at the highest dose levels tested, consistent with the pharmacology of AZD1208 and PIM-2 inhibition.

Overall, 5 patients had a reduction in circulating blasts only, while 2 patients also had a modest reduction in bone marrow blasts. Of the 2 patients with marrow reductions, only 1 patient had evaluable PD biomarker samples with no reduction in phosphoprotein levels detected. All 5 patients with decreases in circulating blasts had evaluable biomarker samples and of those, 3 patients showed a robust decrease. However, several patients who did not have a decrease in blasts did show a reduction in 1 or both of the PD markers suggesting that PIM pathway inhibition alone may not be sufficient to impact the disease.

All 3 PIM kinases were expressed in the patient samples at varying levels with PIM-1 levels generally higher than PIM-2 and PIM-3 levels. There was no correlation between the levels of PIM kinase expression and peripheral blast reductions.

Overall, 5 (approximately 11%) patients had a mutation in FLT3 and 1 (2%) patient had a mutation in nucleophosmin. From this small data set, there was no evidence of a relationship between mutation status and clinical response (peripheral blast reductions).

Patients who had a reduction in blasts tended to have normal cytogenetics.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable

Summary of safety results

AZD1208 monotherapy was generally well tolerated in patients with relapsed or refractory AML at doses ranging from 120 mg to 700 mg (the 900 mg dose level was not tolerated due to 2 DLTs of grade 3 rash). The MTD of AZD1208 was not determined as no dose cohort met the criteria of 6 patients evaluable for DLT. Overall, 31 (96.9%) patients experienced an adverse event (AE). The most commonly reported AEs (preferred term [PT]) were nausea and diarrhea. No clear differences were observed among treatment groups in the frequency of any individual AE. Overall, 24 (75%) patients experienced an AE of CTCAE grade 3 or higher; the most commonly reported of these AEs (PT) were febrile neutropenia, hypotension, and pneumonia. No deaths other than those which were disease related were observed during the study, and these were judged by the investigator to not be causally related to AZD1208. A total of 23 (71.9%) patients experienced serious AEs (SAEs) during the study and the most commonly reported SAEs were febrile neutropenia, hypotension, abdominal pain, maculo-papular rash and back pain. Overall, SAEs judged by the investigator as causally related to AZD1208 were reported in 5 (15.6%) patients. Serious AEs of Guillain-Barre syndrome and increased blood creatinine were each reported in 1 patient in the AZD1208 700 mg dose cohort and febrile neutropenia, rash and maculo-papular rash were each reported in 1 patient in the AZD1208 900 mg dose cohort. There were no findings of clinical concern for vital signs, electrocardiogram, haematology or clinical chemistry parameters.