AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD4877
Study Code	D2782C00007
Edition Number	1
Date	14 January 2010

A Phase I/II, Open-label, Multi-center, Two-part Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of AZD4877 Administered on Days 1, 2 and 3 in Adult Patients with Recurrent or Refractory Acute Myelogenous Leukemia (AML) Excluding Promyelocytic Leukemia

Study dates:	First patient enrolled: 31 July 2007 Last patient completed: 22 July 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.

Publications

An abstract of preliminary results of this study has been published:
Borthakur G, Faderl S, Ravandi F, Padmanabhan S, Stock W, Wu K, et al. A Phase 1/2 multicenter study to assess the safety, tolerability, and pharmacokinetics/dynamics of AZD4877 administered on a daily × 3 schedule in adult patients with refractory acute myelogenous leukemia (AML). J Clin Oncol 2009;27(15s):(Suppl;abstr 3580).

Objectives and criteria for evaluation

The primary and secondary objectives and outcome variables for this study are shown in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
Part A: To identify an MTD of AZD4877 on a daily × 3 schedule by assessment of the incidence of DLTs.	Incidence of DLTs during the initial 15-day period, relative to the first dose of AZD4877 in Part A.
Part B: To assess the effect of AZD4877 on the rate of CR including CRi in patients with first or second relapsed AML, with CR and CRi defined by changes from baseline in bone marrow and blood myeloblast counts and recovery of normal hematopoiesis.[a]	Standardized assessment of marrow response using modified Cheson response criteria for AML (Cheson et al. J Clin Oncol 2007;25:579-86). Relevant response assessment categories were CR and CRi as assigned by the study investigators.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Parts A and B: To determine the pharmacokinetic (PK) profile of AZD4877 administered on a daily × 3 schedule by the assessment of the following PK variables: C_{max}, C_{24h}, AUC, $AUC_{(0-t)}$, $t_{1/2}$, and $t_{1/2\lambda z}$.	Calculation of C_{max}, C_{24h}, AUC, $AUC_{(0-24)}$,[b] and $t_{1/2}$ following dosing on Day 3.
Secondary	**Secondary**
Part B: To assess the effect of AZD4877 on duration of CR or CRi following completion of treatment 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 or molecular abnormality, the reappearance of new dysplastic changes, or the reappearance or development of extramedullary leukemia.[a]	No secondary efficacy variables were derived to support this objective.[a]
Part B: To assess the effect of AZD4877 on rate of CR, CRi, PR, and overall response (CR, CRi, or PR).[a]	Investigator assessment of AML clinical response categories (CR, CRi, PR, disease recurrence post CR, NE, treatment failure [due to resistant disease, due to complications from aplasia, or due to indeterminate cause]). No other secondary efficacy variables were derived to support this objective.[a]
Parts A & B: To evaluate the safety and tolerability of AZD4877 on a daily × 3 schedule by assessment of Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) grade and type of an AE, and changes in non-hematologic laboratory values and vital signs.	During Parts A and B: Study drug exposure; incidence and types of DLTs, AEs, deaths, SAEs, DAEs, OAEs; maximum CTCAE Grade for AEs; change from baseline to worst CTCAE grade on treatment for non-hematological laboratory variables; vital signs changes; and categorical summaries of QT, QTcF, and QTcB on ECGs.
Parts A and B: To seek preliminary evidence of the anti-leukemic activity of AZD4877.	Investigator assessment of AML clinical response (CR, CRi, PR, progressive disease, NE, and NA) during Part A. AML-specific events: CTCAE Grade 1-3 infection or hemorrhage and Grade 1-4 hematology variables.

AE Adverse event; AML Acute myelogenous leukemia; AUC0-t Area under the concentration-time curve to the last quantifiable plasma concentration; C24h Plasma drug concentration 24 hours after administration of a given dose area under the concentration-time; Cmax Maximum plasma (peak) drug concentration after single-dose administration; CR Complete response; CRi Complete response with incomplete blood count recovery; CTCAE Common Terminology Criteria for Adverse Events (Version 3.0); DAE Discontinuation due to an adverse event; DLT Dose-limiting toxicity; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; LVEF Left ventricular ejection fraction; MTD Maximum tolerated dose; NA Not applicable; NE Not evaluable; OAE Other significant adverse event; PK Pharmacokinetic; PR Partial remission; QTcB QTc Bazett; QTcF QTc Fridericia; SAE Serious adverse event; t1/2 Half-life; and t1/2λz half-life associated with terminal slope (λz) of a semi logarithmic concentration-time curve.

[a] The study was terminated early for lack of efficacy after preliminary assessment of the response data from the first 8 patients treated in Part B. Therefore, no efficacy variables were derived programmatically.

[b] $AUC_{(0-t)}$ was originally to be derived as per the study protocol and objectives. That parameter was replaced by $AUC_{(0-24)}$ because the times for the last quantifiable plasma concentration samples after the Induction Course 1 Day 3 dose, but prior to the Induction Course 1 follow-up visit, varied greatly between the patients.

Exploratory and optional objectives

Several exploratory objectives that related to Parts A and B, plus an optional objective, were to be assessed per the study protocol. Samples were collected for each of these objectives;

however, with the exception of Exploratory Objective 3 (presence of monoasters), analyses of these objectives will not be reported. These exploratory objectives included:

Parts A and B:

1. To examine the relationship between clinically significant non-marrow toxicities, marrow aplasia incidence, and duration and plasma exposure of AZD4877 by evaluation of adverse events (AEs), marrow status, and pharmacokinetic (PK) parameters.

2. To correlate leukemia biologic characteristics and clinical outcome by evaluation of exploratory markers of mitosis and the spindle checkpoint, gene expression, centrosome/ploidy status, mitotic index, and P-glycoprotein expression obtained from baseline marrow aspirate samples and correlation with anti-leukemic activity, safety, and PK parameters.

3. To seek preliminary evidence of mechanism of action in hematopoietic cells by assessing the presence of monoasters in bone marrow and/or peripheral circulating mononuclear cells.

4. To seek preliminary evidence of serum markers of leukemia cell death by measuring circulating nucleosomal DNA.

5. To seek preliminary evidence of serum markers of epithelial cell death due to gastrointestinal toxicity by measuring serum levels of M30 and M65 epitopes.

Optional:

To obtain a buccal swab sample for DNA extraction for subsequent, retrospective pharmacogenetic analysis in consenting patients.

Design

This was a 2-part (Part A [dose-escalation] and Part B [clinical response]) study to evaluate the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of AZD4877 (daily x 3) administered on an every two week schedule. The designs of Parts A and B were the following:

Part A - Dose-escalation

Part A was an open-label, dose-escalation (2, 4, 7, 10, 13, 16, and 18 mg) study to determine the maximum tolerated dose (MTD) and explore the safety, tolerability, and PK effect of AZD4877. The MTD was pre-specified as the dose level where 0 or 1 patients experienced a DLT with at least 2 patients experiencing a DLT at the next higher dose level. Prior to each dose escalation, the Investigators and AstraZeneca reviewed the specified safety and tolerability data from all evaluable patients in the dose cohort. When

the MTD was established, a minimum of 6 evaluable patients were to be treated at that dose in Part A before Part B of the study initiated enrollment.

Part B - Clinical-response

Part B was a Phase II, open-label, 2-stage study to assess the efficacy of AZD4877 and to further characterize the safety, tolerability, PK, and pharmacodynamic (PD) effects of the drug. The dose used in Part B was to be either the MTD determined in Part A or a dose below the MTD that was selected by the investigators and AstraZeneca after considering previous safety and tolerability data.

Part B followed a Simon optimal 2-stage design (Simon R. Control Clin Trials 1989;10:1-10) based on the rate of complete response (CR) or CR with incomplete blood count recovery (CRi). Nineteen patients were to be treated during the first stage of Part B. If 3 or fewer patients achieved a CR or CRi, the study was to be stopped for lack of efficacy. If 4 more patients achieved a CR or CRi, an additional 14 patients were treated. This design had 90% power overall and a 10% chance of a false negative result. A false negative result corresponded to failing to accept a treatment with a CR+CRi rate of 35% or more at the end of either stage of Part B.

Both Parts A and B consisted of an induction remission phase and a consolidation treatment phase. In the induction remission phase, one or two 3-day treatment courses were administered at approximately 2-week intervals. Following the initial induction course, a decision regarding the timing of the second course was made based on clinical assessments including circulating blood cell counts, a bone marrow aspirate if clinically indicated, and the patient's overall clinical status.

In the consolidation treatment phase, patients who achieved a complete remission (CR or CRi) after one or two 3-day induction courses had the option to continue in the study and receive up to four 2-day consolidation courses with AZD4877 provided that no withdrawal criteria were met and that significant toxicity, if it occurred, was believed by the investigator to have been both manageable and acceptable. Each successive consolidation course was given 7 to 21 days after recovery of circulating blood cell counts to Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 Grade 0 or 1, and when the patient was clinically stable. During consolidation treatment, patients received AZD4877 at their originally assigned dose with modification as deemed clinically necessary.

Patients who withdrew from study treatment were followed up for safety, where possible, for up to 30 days after last administration of AZD4877.

Early termination of study

The initial recruitment into Part B of this study was rapid and, in this open-label study, preliminary response data was being reported in an ongoing, unvalidated manner by the sites. On 29 May 2009, recruitment into the study was suspended to enable a preliminary assessment of the response data from the first 8 patients treated in Part B. Based on

unvalidated reports from the sites, none of the 8 patients had experienced a CR or CRi. A response rate of 0 out 8 corresponded to a 3% false negative risk; therefore, on 16 June 2009, the study was terminated early for lack of efficacy. The study was not terminated for safety reasons.

Target population and sample size

This study enrolled patients ≥18 years of age with relapsed or refractory acute myelogenous leukemia (AML), excluding acute promyelocytic leukemia. Patients enrolled in Part A had AML for which no standard therapies were anticipated to result in a durable remission. The projected maximum number of patients enrolled in Part A was approximately 30.

Patients enrolled in Part B had AML with a maximum of 2 prior relapses or failure to achieve remission after at least 1 attempt at induction treatment. Part B followed the Simon optimal 2-stage design (Simon 1989), which minimized the expected sample size based on the rate of CR+CRi. A rate of CR+CRi ≤15% was considered low, and a rate of CR+CRi of ≥35% was considered desirable. The desired Type 1 and Type 2 errors are ≤0.10, 1-sided. Under these constraints, the Simon 2-stage design required the enrollment of 19 evaluable patients during the first stage of Part B, and that enrollment would stop for lack of efficacy if 3 or fewer patients achieve a CR or CRi. If 4 or more patients achieved a CR or CRi, an additional 14 patients were to be enrolled. Achievement of a CR or CRi in 8 or more of the 33 patients was considered an indication of efficacy. Thus, a minimum of 19 evaluable patients and a maximum of 33 evaluable patients were anticipated for enrollment in Part B.

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

AZD4877 concentrate (5 mg/mL) was diluted in 250 or 500 mL 0.9% sodium chloride to ensure a concentration ≤0.4 mg/mL; it was administered as a 1-hour intravenous infusion. The Formulation Number for this open-label investigational product was F13438; the Batch Numbers were P/4158/19 and P/4158/25A.

Statistical methods

Due to early termination of Part B, no formal statistical analyses of the rates of CR, CRi, or any other efficacy variables were conducted. Because of sample size limitations in Parts A and B, statistical analyses were restricted to summaries of all data from all treated patients to assess safety, tolerability, PK, PD, and initial indications of anti-leukemic activity of AZD4877. Clinically significant changes from baseline were assessed for vital signs, electrocardiograms (ECG), and non-hematological laboratory safety variables.

Patient population

Forty-seven patients were enrolled in the study. Of these, 39 patients received at least 1 dose of AZD4877 and were evaluable for safety: 30 patients participated in Part A (2 mg=6 patients, 4 m=3 patients, 7 mg=4 patients, 10 mg=3 patients, 13 mg=3 patients; 16 mg=7 patients, 18 mg=4 patients); and 9 patients participated in Part B (16 mg). In Part A, 28 of the

30 patients evaluable for safety were also evaluable for DLT and PK assessments (the 2 excluded patients had received <3 doses of AZD4877 [1 patient who received the 2-mg dose and 1 patient who received the 16-mg dose]). In Part B, all 9 patients evaluable for safety were also evaluable for efficacy and PK assessments.

Patients in the safety analysis set (n=39) had a mean age of 62.4 years (range: 23 to 84 years). Approximately one-half of the patients were <65 years of age (n=19), and the majority were white (n=32). More men (n=26) than women (n=13) participated in the study.

The most common reason for discontinuation from the study was a lack of therapeutic response. No major protocol deviations occurred; however, several patients had PK-related deviations (such as infusion durations outside the allowed time window or missing, or sampling times outside the allowed time window or missing) that affected the calculation of the PK parameters.

Summary of pharmacokinetic results

Thirty-seven patients had evaluable PK data obtained following the first induction course on Day 3. A summary of the AZD4877 PK parameters assessed is presented in Table S2.

Table S2 Summary of AZD4877 pharmacokinetic parameters following Induction Course 1 on Day 3 (PK analysis set)

Variable (unit)	Summary Statistic	AZD4877 actual Day 1 dose								
		Total (N=37)	2 mg (N=5)	4 mg (N=3)	7 mg (N=4)	10 mg (N=3)	13 mg (N=3)	16 mg Part A (N=6)	16 mg Part B (N=9)	18 mg (N=4)
C_{max} (ng/mL)	n	31	3	2	4	3	3	5	7	4
	Gmean	71.2	11.3	19.3	41.9	123	114	99.4	87.1	200
	CV (%)	168	9.43	22.1	45.6	157	59.2	24.2	130	92.2
C_{24h} (ng/mL)	n	30	5	2	4	2	3	5	5	4
	Gmean	13.2	2.88	4.51	7.97	12.3	19	23.4	23.3	48
	CV (%)	148	72.6	85.6	29.6	14.3	74.5	28.2	18.1	114
AUC (ng*h/ mL)	n	6	0	0	3	0	1	2	0	0
	Gmean	860	NC	NC	750	NC	571	1290	NC	NC
	CV (%)	42.8	NC	NC	53.1	NC	NC	0.822	NC	NC
$AUC_{(0-24)}$ (ng*h/ mL)	n	33	5	2	4	2	3	6	7	4
	Gmean	521	112	129	439	402	842	729	921	1520
	CV (%)	117	61.7	76	60.4	3.11	65.2	21.1	127	48.3
$t_{1/2}$ (h)	n	6	0	0	3	0	1	2	0	0
	Arimthetic mean	17.1	NC	NC	16.7	NC	18.9	17.0	NC	NC

AUC Area under the concentration-time curve; $AUC_{(0–24)}$ Area under the concentration-time curve time 0 to 24 hours; C_{24h} Plasma concentration at 24 hours; C_{max} Maximum plasma concentration; CV Coefficient of variation; n Number of patients with calculable values for each variable; N Number in group; NC Not calculable; $t_{1/2}$ Half-life.

Over the dose range studied (2 to 18 mg), systemic exposure of AZD4877 (C_{max}, AUC, and C_{24h}) generally increased with dose. Although exposure is variable across the dose range, it is generally consistent with data from other AZD4877 clinical studies. The mean terminal half-life values, where calculable (16.7 to 18.9 hours), appeared to be independent of dose.

Summary of safety results

In the safety analysis population, 22 patients received a single, complete, 3-day induction course (including 5 patients in Part B). An additional 2 patients who initiated the first induction treatment did not complete the course (1 patient because of voluntary discontinuation and 1 patient because of an AE). Fifteen patients received 2 induction courses (including 5 patients in Part B). One patient in Part B had a dose reduction from 16 mg to 13 mg during the second induction course. Two patients (1 patient who received the 7-mg dose and 1 patient who received the 10-mg dose) proceeded to receive 2 consolidation courses each, although neither patient achieved a CR or CRi during the consolidation treatment. The median number of doses of AZD4877 in the study as a whole was 3 (range: 1 to 10 doses), and the median total dose (mg) received was 48 mg (range: 2 to 108 mg).

The MTD of AZD4877 for patients with AML in this study was 16 mg daily × 3.

During the first 15 days of treatment, 3 patients experienced a total of 4 adverse events that were considered DLTs by the investigator. Table S3 summarizes the results of dose decisions based on DLTs that began within 15 days of the first dose of AZD4877.

Table S3 Summary of cohorts and dose escalation based on DLTs (safety analysis set)

Cohort	Assigned Day 1 AZD4877 dose (mg)	n	Number of evaluable patients	Number of evaluable patients with a DLT	DLT (MedDRA preferred term)/ CTCAE Grade
Part A					
1	2	6	5	0	
2	4	3	3	0	
3	7	4	4	0	
4	10	3	3	0	
5	13	3	3	0	
6	18	4	4	2	Palmar-Plantar Erythrodysesthesia Syndrome/Grade 3 Stomatitis/Grade 3
7	16	7	6	1	Hyperbilirubinemia/Grade 3 and Stomatitis/Grade 3
Part B					
	16	9	9	0	

CTCAE Common Terminology Criteria for Adverse Events (Version 3.0); DLT Dose-limiting toxicity; MedDRA Medical Dictionary for Regulatory Activities (Version 12.1).

All 39 patients in the safety analysis set had at least 1 AE. The most commonly reported AEs (occurring in ≥30% of patients) by Medical Dictionary for Regulatory Activities (Version 12.1; MedDRA) were diarrhea (n=18), hypokalemia (n=16), nausea (n=14), fatigue (n=12), and hypocalcemia (n=12).

Table S4 presents the CTCAE Grade ≥3 AEs that occurred in 2 or more patients by MedDRA preferred terms. Of the 24 patients who reported CTCAE Grade ≥3 AEs, 10 had events that were considered by the investigator to be causally related to treatment.

Table S4 CTCAE Grade ≥3 adverse events occurring in 2 or more patients, by MedDRA-preferred term (safety analysis set)

Variable	Dose (n)								
	Total (N=39)	2 mg (n=6)	4 mg (n=3)	7 mg (n=4)	10 mg (n=3)	13 mg (n=3)	16 mg Part A (n=7)	16 mg Part B (n=9)	18 mg (n=4)
Patients with any AE of CTCAE Grade ≥3[a]	24	6	0	2	2	1	5	4	4
Hypokalemia	8	0	0	0	1	1	3	2	1
Hypophosphatemia	3	0	0	1	0	0	1	1	0
Stomatitis	3	0	0	0	0	0	1	0	2
Fatigue	2	1	0	0	1	0	0	0	0
Mucosal inflammation	2	0	0	0	0	0	0	2	0
Dysphagia	2	0	0	0	1	1	0	0	0
Pneumonia	2	1	0	1	0	0	0	0	0
Hyperbilirubinemia	2	1	0	0	0	0	1	0	0

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events (Version 3.0); DLT Dose-limiting toxicity; MedDRA Medical Dictionary for Regulatory Activities (Version 12.1); N Total number of patients; n Number of patients in the treatment group.

[a] Patients could have had more than 1 Grade ≥3 adverse event.

Six patients died due to disease progression during the study. Two of these patients had fatal serious adverse events (SAEs) that were reported as secondary causes of death: 1 patient who received the 2-mg dose had a cerebral hemorrhage, and 1 patient who received the 10-mg dose had fungal pneumonia).

A total of 13 patients reported SAEs. The only SAE that occurred in more than 1 patient was mucosal inflammation, which was reported by 3 patients in Part B (16 mg). Seven patients had SAEs that were considered by the investigator to be causally related to AZD4877 (atrial flutter; diverticulitis and hyperbilirubinemia; mucosal inflammation [2 separate patients]; mucosal inflammation and Stevens-Johnson Syndrome; Palmer-Planter Erythrodysesthesia Syndrome; stomatitis).

One patient discontinued the study due to an AE of hyperbilirubinemia that was considered by the investigator to be causally related to study treatment.

Twenty-three patients had CTCAE Grade 3 or 4 clinical chemistry values. The majority of the Grade 3 or 4 events were low albumin, high potassium, or high magnesium. There was no apparent dose-response relationship. The abnormalities that occurred were consistent with those typically found in a population of patients with refractory recurrent AML. No clinically significant treatment-emergent changes in vital signs or ECGs were noted.

Summary of efficacy/anti-leukemic activity results

There were no reported AML responses of CR, CRi, or partial remission (PR) during Parts A or B of the study. In Part B, all 9 patients had treatment failure due to resistant disease.

Summary of pharmacodynamic activity

Twelve patients provided peripheral blood samples that were evaluable for monoaster determination during the first 28-day induction period; no adequate bone marrow smears for monoaster assay were obtained. For these patients, monoasters were observed at the 2, 7, 10, 13, 16, and 18 mg doses (none were detected at the 4-mg dose). Specifically, monoasters were detected on Day 1 at 6 hours (± 1 hour) after beginning AZD4877 treatment in 9 patients (2 mg=1 patient, 7 mg=1 patient, 10 mg=1 patient, 13 mg=1 patient, 16 mg [Part A]=3 patients, 18 mg=2 patients), and on Day 2 (24 hours after completion of the Day 1 treatment) in 4 patients (16 mg [Part A]=2 patients, 18 mg=2 patients).