Drug Substance	AZD4877	**SYNOPSIS**	(For national authority use only)
Study Code	D2782C00002		
Edition Number	1		
Date	12 December 2007		

A Phase I, Open-Label, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD4877 Administered Once Weekly in Adult Patients with Recurrent or Refractory Acute Myelogenous Leukemia (AML), Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia (Ph negative ALL), Aggressive Non-Hodgkin Lymphoma (NHL) or Multiple Myeloma (MM)

Study dates

First subject enrolled 14 March 2007

Last subject completed 9 August 2007

Phase of development

Clinical pharmacology (I)

Early termination of study

Study D2782C00002, was a Phase 1 study to evaluate the safety, tolerability and pharmacokinetics of AZD4877 given weekly. The first patient was enrolled into the study on 14 March 2007. On 9 August 2007, a decision was taken and communicated to investigators to prematurely terminate the study. It is important to emphasize that there were no safety issues identified in this trial. A decision to close Study D2782C00002 was made due to very slow patient accrual and continued delays in activating study sites. Another AZD4877 study in patients with hematologic tumors (recurrent or refractory acute myelogenous leukemia excluding promyelocytic leukaemia), Study D2782C00007, enrolled its first patient on 31 July 2007 and has demonstrated favorable recruitment with a daily x 3 dosing regimen.

Objectives

Primary Objectives:

- To identify a maximum tolerated dose (MTD) of AZD4877 on a weekly schedule in patients with recurrent or refractory leukemia, lymphoma or multiple myeloma (MM) by assessment of incidence of dose-limiting toxicities (DLTs)

- To determine the pharmacokinetic (PK) profile of AZD4877 by measurement of maximum plasma (peak) drug concentration after single-dose administration ($C_{max)}$, plasma drug concentration at 24 hours after administration of a given dose (C_{24h}), and area under the plasma concentration-time curve from zero to infinity (AUC) following the dose of AZD4877 on Cycle 1, Day 1

Secondary Objectives:

- To evaluate the safety and tolerability of AZD4877 by assessment of Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) grade and type of adverse event (AE), changes in laboratory values, vital signs and incidence of protocol-defined dose modifications or omissions due to adverse events

- To determine the pharmacokinetic (PK) profile of AZD4877 by measurement of area under the plasma concentration-time curve to the last quantifiable plasma concentration ($AUC_{(0-t)}$), total body clearance of drug from plasma (CL), half-life associated with terminal slope (λ_z) of a semi-logarithmic concentration-time curve ($t_{½\lambda z}$), mean residence time (MRT), renal clearance of unchanged drug from plasma (CL_r), cumulative amount of unchanged drug excreted into urine (A_e), and volume of distribution at steady state (V_{ss}) obtained following the dose on Cycle 1, Day 1

- To seek preliminary evidence of the anti-tumor activity of AZD4877.

- To seek evidence of the mechanism of action in bone marrow and/or peripheral circulating mononuclear cells by detection of monoasters

Exploratory Objectives:

- To seek preliminary evidence of plasma markers of tumor cell death by measuring circulating nucleosomal DNA, and epithelial cell death due to gastrointestinal (GI) toxicity by measuring Plasma M30 and M65

- To examine the relationship between toxicity, particularly GI toxicity, and AZD4877 plasma exposure by correlating adverse events and PK parameters

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

Optional: In consenting patients, to obtain a buccal scrape sample for DNA extraction for subsequent, retrospective pharmacogenetic analysis.

Study design

This was a Phase 1, open-label, multicenter, dose-escalation study to evaluate the safety, tolerability and pharmacokinetics of AZD4877 given weekly. In addition, this study included the following exploratory objectives: proof of mechanism, markers of cell death, correlation of tumor biologic characteristics with anti-tumor activity, and relationship between toxicity and exposure. No protocol amendments were approved by the Institutional Review Boards or implemented in this study.

Initial dose used was 5 mg, which was the mid-dose 1/10th the severely toxic dose (STD10) in pre-clinical toxicology studies. Mid-dose was used as the observed toxicities were considered potentially gender-specific in that female rats had greater toxicity than males. Dose escalation was to occur by doubling the dose from the previous dose (10 mg, 20 mg, etc.) until a Grade 2 adverse event was seen, and then by 50% or 25% increases based on prior safety and tolerability.

Six evaluable patients were to be enrolled at each dose level. Dose escalation decisions were to be made after 4 evaluable patients reached Cycle 1, Day 28, and 2 additional patients had at least one dose of study drug and completed one week of follow-up. At the time of dose escalation decision, all safety data from all enrolled patients at a given dose level was to be considered.

Enrollment of patients was to continue until the maximum dose was identified at which 0 or 1 patients experienced a dose-limiting toxicity at a given dose level. This dose was to be considered the maximum tolerated dose (MTD).

Target subject population and sample size

Depending on the number of dose escalations required and number of patients in the dose cohorts, the projected maximum number of patients to be enrolled was 75. A total of

5 patients (at 2 centers) were enrolled. Patients with recurrent or refractory advanced hematologic malignancies for which standard curative or palliative measures do not exist or are no longer effective were eligible. Specifically, patients with morphologically and, where appropriate, phenotypically confirmed hematologic malignancies of any of the following: AML, Philadelphia chromosome (Ph chromosome)-negative ALL, aggressive non-Hodgkin lymphoma (NHL) (includes diffuse large B-cell lymphoma, mediastinal large B-cell (or Burkitt) lymphoma, T or B lymphoblastic lymphoma, peripheral T-cell lymphoma and anaplastic large cell T- or Null-cell lymphoma), or MM.

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

AZD4877 was administered as a one-hour intravenous (IV) infusion of 5 mg. The following AZD4877 batches were used in this study: 2000102121 (for Site 4 in Canada) and 2000100281 (for Site 11 in the United States).

Duration of treatment

AZD4877 was administered intravenously over 1 hour on Days 1, 8, and 15 of each 28-day cycle (3 weeks of treatment plus 1 week of rest). Following the completion of Cycle 1, during either the dose-escalation or expansion phase, individual patients could receive consecutive treatment cycles provided that: (1) they were continuing to benefit; (2) there was no evidence of disease progression (isolated meningeal relapses were excluded); (3) they did not meet any other withdrawal criteria; and (4) if a DLT had occurred, the investigator believed it was both manageable and acceptable. Patients received AZD4877 on their originally assigned dose with modifications as deemed clinically necessary. An individual patient could have the cycle dose increased to the next higher dose only and dose escalation could only be done when this dose has been evaluated and ≤1 DLT had occurred in the dose cohort.

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

Variables

- Pharmacokinetic

The following PK parameters of AZD4877 were obtained from Cycle 1: C_{max}, C_{24h} and AUC, $AUC_{(0-t)}$, CL, CL_r, A_e, $t_{½\lambda z}$, MRT and V_{ss}.

- Anti-tumor activity

Anti-tumor activity was to be measured by: marrow response using Cheson criteria in AML, standard criteria in lymphocytic leukemias in ALL and aggressive lymphomas, and combined EBMT, IBMTR and ABMTR myeloma criteria in multiple myeloma. In patients with a solid tumor component, tumor change was to be assessed using Response Evaluation Criteria in Solid Tumors [RECIST]. Tumor reduction that did not meet criteria for partial regression in solid tumor, or marrow complete or partial remission were to be noted. Changes in non-measurable tumor were also to be noted. Tumor reduction that did not meet criteria for partial

regression in solid tumor, or marrow complete or partial remission, were to be noted. Changes in non-measurable tumor were also to be noted.

- **Pharmacodynamic**

The following pharmacodynamic variables were to be collected and evaluated:

- Proof of mechanism/cell death markers
- Correlate tumor biologic characteristics and clinical outcome
- Pharmacogenetics

- **Safety**

- Assessment of CTCAE grade and type of AEs and DLT
- Changes in laboratory values
- Changes in vital signs
- Plasma hemoglobin

Statistical methods

Because of sample size limitations, statistical analysis is restricted to simple summaries and listings of safety, tolerability, PK, and disease progression data. The data for proof of mechanism (monoasters), cell death markers, and other exploratory biomarkers are not presented in this report.

Changes of analysis from protocol

AZD4877 concentration in urine, including the derived parameters CL_r and A_e, was not analyzed due to inadequate urine collection procedures: AZD4877 was discovered to bind to the plastic urine collection containers.

Anti-leukemic activity variables were not summarized, as no such activity was seen.

As only 4 patients received study treatment, results are listed for most variables, but descriptive statistics and summary presentations are presented for only select variables (eg, AEs).

As only one dose level of AZD4877 was administered in this study, no dose-response modeling was conducted.

RESULTS

Subject population

Of the 5 patients enrolled in the study, 4 received at least one dose of AZD4877 and are included in the 'safety set.' The study was terminated before the fifth patient began Cycle 1. All 4 dosed patients also had evaluable pharmacokinetic samples and are included in the 'pharmacokinetic set', and 3 of the 4 patients met the protocol-defined criteria for evaluability for dose-limiting toxicity. Summary tables and listings are based on either the safety or pharmacokinetic set of patients.

The 4 patients dosed had a mean age of 60 years (range 47 to 70 years), were White, and comprised 3 women and 1 man. Three of the 4 patients had Acute Myelogenous Leukemia and 1 had Multiple Myeloma. These patients had received 3 to 6 regimens of cancer therapy prior to enrollment in this study. None had received prior radiotherapy.

Two patients (Patients E0004001 and E0004003) completed only 1 week of Cycle 1, one patient (Patient E0011001) completed Cycle 1, and one patient (Patient E0004002) completed 2 full cycles of treatment. Three patients withdrew from the study due to progressive disease and one patient (Patient E0004001) withdrew due to a DLT (sepsis and intestinal perforation). However, Patient E0004003, who withdrew due to disease progression, did so after only one week of treatment and; therefore, was not evaluable for dose-limiting toxicity (DLT).

Summary of anti-tumor activity

There were no signs of anti-tumor activity of AZD4877 at the low dose administered in this study. Samples collected for exploratory pharmacodynamic variables (eg, plasma cell death markers) were analyzed and archived, but were not entered in the study database and no results are presented in this report.

Summary of pharmacokinetic results

Available concentration data suggested that AZD4877 PK in humans was consistent with predictions from nonclinical PK for AZD4877; however, due to the small number of patients in this trial, were not sufficient to establish the PK profile in this patient population. Aside from one apparent outlier C_{max} value (89.2 ng/mL in Patient E0004002), C_{max} values were 14.1 to 24.8 ng/mL. Values for C_{24h} (n=4) were 1.97 to 3.03 ng/mL, AUC values (n=3) were 203 to 267 ng.h/mL, and $t_{½\lambda z}$ (n=3) were 14.4 to 17.3 hours. Urine PK assessments could not be done as AZD4877 was discovered to bind to the plastic urine collection containers.

Summary of safety results

One death, all SAEs, and all DAEs reported during this study occurred in 2 patients (Patients E0004001 and E0004003). None of the SAEs (fatal or non-fatal) or DAEs were considered by the investigator to be drug-related. One patient (Patient E0004003) died as a result of disease progression (increased white blood cell count) and one patient (Patient E0004001) had protocol-defined dose-limiting toxicity of CTCAE Grade 4 infection (sepsis and intestinal perforation). These 3 events (increased white blood cell count, sepsis, and intestinal perforation) comprised all 3 SAEs and all 3 DAEs in the study. Three patients (Patients

E0004001, E0004002, and E0004003) had at least one AE with a maximum CTCAE Grade ≥3. The 4 drug-related AEs observed (dizziness in Patient E0004001, and diarrhea, nausea, vomiting in Patient E0004002), were CTCAE Grade 1 or 2, and were consistent with the expected safety profile of AZD4877. There were no AEs relating to hypertension or prolonged QT interval, nor any notable changes in electrocardiograms (ECGs) or vital signs.

Laboratory data showed 3 of the 4 patients to have CTCAE Grade 3 or 4 abnormalities (Patients E0004001, E0004002, and E0004003). These abnormalities reflected mainly leukaemia, disease management complications, and/or infection. None were considered by the investigator to be drug-related. Patient E0004001 had CTCAE Grade 3 or 4 hypocalcaemia, troponin elevation, and hypokalaemia. Patient E0004002 had hypokalaemia. Patient E0004003 had hypokalaemia, hypophosphataemia, increased white blood cell count, elevated aspartate aminotransferase (AST), and elevated alkaline phosphatase. This patient also had CTCAE Grade 3 mucositis.