AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8330
Study Code	D1536C00001
Edition Number	1
Date	30 September 2011

A Phase I, Open-Label, Multi-centre Study to Assess the Safety, Tolerability and Pharmacokinetics of Single and Multiple Oral Doses of AZD8330 in Patients With Advanced Malignancies

Study dates: First subject enrolled: 21 March 2007
Last subject enrolled: 14 April 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 centres in USA (Fox Chase Cancer Centre and M.D. Anderson Cancer Centre) and one centre in Norway (Radiumhospitalet Comprehensive Cancer Centre).

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
Primary	**Primary**
To assess the safety and tolerability of AZD8330 in patients with advanced malignancies.	Adverse Events, clinical chemistry (including BNP or NT-proBNP), haematology, coagulation, and urinalysis. Vital signs, MUGA scans/echocardiography, electrocardiograms (ECGs), ophthalmologic examination, O2 saturation.
Secondary	**Secondary**
To determine the pharmacokinetics (PK) of AZD8330 following both single and multiple oral dosing of AZD8330 in patients with advanced malignancies.	Derived pharmacokinetic parameters for AZD8330 will be produced following both a single and multiple oral dosing. This may include Cmax, tmax, CL/F and t½.
To investigate possible relationships between plasma AZD8330 concentrations/exposure and changes in safety and pharmacodynamic parameters.	Output from both graphical and/or appropriate PK/pharmacodynamic modelling techniques.
To investigate the effect of AZD8330 treatment on pERK in PBMCs in patients with advanced malignancies.	Change in biomarker pERK in PBMCs.

BNP: b-type natriuretic peptide, NT-proBNP: N-terminal prohormone b-type natriuretic peptide, MUGA: multiple gated acquisition scan, Cmax: maximum plasma concentration, tmax: time to reach maximum plasma concentration, CL/F: total apparent drug clearance, t½: half life, pERK: phosphorylated extracellular signal-regulated kinase, PBMC: peripheral blood mononuclear cell (leucocyte ghosts).
Exploratory objectives from the clinical study protocol (CSP) are not reported in the clinical study report synopsis.

Study design

The study was initially designed to have two parts. Protocol Amendment 4 dated 5th August 2008 removed Part B from the study and no patients were enrolled in part B.

Part A: Dose escalation phase

- Part A aims to define the maximum tolerated dose (MTD) of AZD8330, and in the process collect data to allow evaluation of safety, tolerability and pharmacokinetics (PK) during the escalation phase. Six to nine patients were enrolled per cohort.

The design as described provided the required information to define the maximum tolerated dose (MTD) of AZD8330 following once daily (o.d.) or twice daily (b.d.) dosing in Part A of the study.

Target patient population and sample size

Male and female patients aged 18 years or older who had a cancer that was refractory to standard therapies or for which no standard therapies exist. Inclusion is irrespective of stage of disease.

For the dose escalation phase, a minimum of 6 and a maximum of 9 evaluable patients were recruited in each cohort with 11 cohorts completed. In total, 110 patients were enrolled (including screen fails), 82 patients were treated across 11 cohorts.

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

AZD8330 tablets were supplied in 0.5 mg, 0.75 mg, 1.5 mg and 5 mg strengths, for oral administration.

Batch numbers for AZD8330 tablets:

0.5 mg – P/5376/17, P/5376/07

0.75 mg – P/5376/08

1.5 mg – P/5380/11, P/5225/30, P/5380/11, P/5376/09

5 mg – P/5225/38, P/5254/6, P/5225/31, P/5376/10, P/5376/11

Duration of treatment

The o.d. dosing followed an initial single dose of AZD8330 on day 1 and was followed by a 7-day washout period with daily dosing starting from Day 8. For b.d. dosing AZD8330 was administered b.d. on Day 1 and was followed by a 7-day washout period with b.d. dosing starting from Day 8.

For the safety review meetings at least 6 patients needed to complete at least 35 days of treatment.

Patients continued to receive AZD8330 until disease progression in the opinion of the investigator and as long as they were continuing to derive benefit from treatment.

Statistical methods

No formal statistical analysis was performed. The data is summarised using descriptive statistics, and where appropriate, graphical displays.

Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities Version 13.1, and graded using Version 3 of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAC).

Patient population

Table S2 Summary of patient disposition

	Since Study Started*
Number of patients planned for inclusion:	83
Total Entered	83**
Total Treated	82**
Gender	
Male	40
Female	43
Age	
0 - 1 Months – Neonates	
>1 Month - 2 Years – Infants	
>2 - 12 Years – Children	
>12 - 16 Years – Adolescents	
>16 - <65 Years – Adult	55
≥ 65 Years – Elderly	28
Other (specify)	
Race	
Caucasian	67
Black	11
Asian	1
Other (Hispanic)	4
Number Completed	64
Number Discontinued	19

* Data cut off for the study was 6th October 2010.
** 83 patients were entered and 82 patients were treated from 3 centres in 2 countries. 1 patient was a screen fail and has been incorrectly included in the table.

Summary of safety results

The primary objective of this study was to assess the safety and tolerability of AZD8330 and to define the MTD of AZD8330 in patients with advanced malignancies. 77 of 82 patients (93.9%) reported at least one adverse event (AE). In 47 of 82 (57.3%) patients the AEs were considered related to study drug by the investigator. The most frequently reported adverse events regardless of causality were: fatigue (37.8%), diarrhea (29.3%), vomiting (24.4%), decreased appetite (24.4%), constipation (23.2%) and peripheral edema (22.0%). The majority of the reported adverse events were CTCAE Grade 1 or 2. The most commonly reported CTCAE Grade 3 or higher events were: pneumonia (3.7%) and left ventricular dysfunction (3.7%) in 3 patients each.

32 of 82 (39%) patients reported SAEs. The most common SAEs reported to the global patient safety database were small intestinal obstruction verbatim term (reported 4 times with 3 reports experienced by 1 patient). The majority of SAEs reported were not considered by the reporting investigator to be related to AZD8330.

10 patients permanently discontinued study treatment due to an AE. The majority of AEs leading to discontinuation were not considered causally related to AZD8330 in the opinion of the investigator.

10 patients died between Day 13 and 57 of study treatment, all due to disease progression in the opinion of the investigator.

The dose-limiting toxicity (DLT) was mental status changes, with verbatim AE terms reported including “confusion”, “mental status changes” and “hallucinations”. These AEs were considered by the investigators to be related to study drug, and identified and classified as DLTs in both the 40 (2 out of 9 patients) and 60 (1 out of 3 patients) mg o.d cohorts. Although the majority of these events were Grade 2 or less, they were considered to be sufficiently clinically significant in the opinion of the Safety Review Committee to meet the protocol definition of a dose limiting toxicity. The mental status change adverse events that defined AZD8330 non-tolerability were generally reversible by cessation of AZD8330. These adverse events occurred, approximately 15 to 47 days after the first dose of AZD8330, no relationship was observed between exposure, as measured by Cmax and AUC, on Day 1 and 15, and the adverse events defined as mental status changes. Maximal AZD8330 plasma concentrations were observed approximately 0.5 to 1h post-dose and were also not temporally related to the adverse events. In the 20 mg b.d. cohort, one patient experienced a CTCAE Grade 3 rash 19 days after starting treatment with AZD8330. This was considered related to treatment in the opinion of the investigator and a dose-limiting toxicity (DLT).

Marked variability in the cardiac function assessments by MUGA and echocardiogram scans has been observed in study D1536C00001. No significant change in ECG parameters or laboratory abnormalities of Troponin and brain natriuretic peptide (BNP) were reported. An serious adverse event of left ventricular dysfunction in a 68 year old male patient receiving AZD8330 12 mg o.d. had been reported; which was related to study treatment according to the reporting investigator. The patient recovered after study drug discontinuation.

Summary of pharmacokinetic results

Pharmacokinetic (PK) analysis of data from 0.5 to 60 mg AZD8330 o.d. and 20 mg AZD8330 b.d. shows that, after a single dose of AZD8330 absorption was rapid, median t_{max} was 0.5 h across the dose groups, in the fasted state. The terminal elimination half-life ($t_{1/2}$) was approximately 11 h; steady state for AZD8330 was achieved by study Day 15 (i.e. after 8 days of multiple dosing). AZD8330 accumulation upon multiple dosing was minimal. Exposure to AZD8330 increased approximately proportionally with dose for the dose range 0.5 to 60 mg AZD8330.

Following administration of the maximum tolerated dose (20 mg twice daily) the geometric mean and %CV of the C_{max} (n=17) and $AUC_{(0\text{-}12h)}$ (n=4) exposures at steady state were 83.4 ng/mL (71.1%) and 218.6 ng.h/mL (65.8%), respectively.

Summary of pharmacodynamic results

Analytical results of the levels of pERK in human samples from this clinical study are presented in the biomarker contribution report see appendix 12.1.13 without further clinical interpretation.

Of the 82 sample sets received and analysed, 12 sets contained at least one time point where the vehicle and agonist had been switched, this was due to processing errors at the study sites.

Summary of pharmacokinetic/pharmacodynamic relationships

The preliminary PK and the pharmacodynamic assay data (inhibition of phosphorylated ERK (pERK) in PBMCs) for doses of 0.5 to 60 mg AZD8330 have been analysed in a preliminary population PK/PD model. The model predicts that following administration at the MTD AZD8330 o.d. to steady state, the population median inhibition of pERK would be approximately 80 % at the time corresponding to the C_{max}; by 4h post-dose the percentage inhibition of pERK would decline to approximately 40 %.