AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8055
Study Code	D1600C00001
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A Phase I/II, Open Label, Multi-centre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of the Tor Kinase Inhibitor AZD8055 Administered Orally to Patients with Advanced Solid Tumours

Study dates: First subject enrolled: 18 July 2008
Last subject last visit: 29 Nov 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)

This was a multi-centre study conducted at 4 centres, in the UK, USA and France.

Publications

None at the time of writing this synopsis.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the safety and tolerability of AZD8055 in patients with advanced solid tumours (or lymphomas Part A only)	Incidence and severity of adverse events (CTCAE Version 3.0), vital signs, ECG parameters, general organ function, clinical chemistry, haematology, urinalysis, nervous and musculoskeletal system and physical examinations.	Safety
Secondary	**Secondary**	
To determine the pharmacokinetics (PK) of AZD8055 following both single and multiple oral dosing of AZD8055 in patients with advanced solid tumours (or lymphomas Part A only).	Where the data allow, single dose and multiple dose PK parameters will be calculated, which may include but not be restricted to: single dose: Cmax, tmax, t½ , AUC, AUC(0-t), AUC(0-12), CL/F and Vss/F multiple dose: Cmin samples during escalation to steady state, at steady state Cmax ss, tmax ss, Cmin ss, t1/2, AUCss, CLss/F, and accumulation ratio Furthermore, if there are sufficient data, the linearity of exposure will be explored following single dose and also at steady state, the time to steady state will be determined, and the predictability of kinetics from a single dose to multiple dose will be assessed.	PK
To obtain a preliminary evaluation of the role of renal excretion in the disposition of AZD8055	Amount of AZD8055 excreted unchanged in the urine (Ae) in the period immediately following dosing, percentage dose excreted (fe %) and renal clearance (CLR).	PK
To evaluate phosphorylation levels of biomarkers such as, but not limited to, AKT and 4EBP1 following treatment with AZD8055 in PBMCs.	Change in phosphorylation of biomarkers such as, but not limited to, AKT and/or 4EBP1 in PBMCs (isolated from blood samples). All residual biomarker samples may be investigated for other cancer related biomarkers.	Biomarkers

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
To investigate possible relationships between plasma AZD8055 concentrations/exposure and changes in safety and pharmacodynamic (PD) parameters*	Where data permit, the PK (AZD8055 exposure)/PD (eg. changes in biomarkers, safety parameters) relationship will be explored graphically and/or using appropriate PK/PD modelling techniques*	PK/PD
To give an early indication of efficacy by evaluation of tumour size.	Objective Response Rate and Best Overall Response (based on RECIST) for patients with measurable disease. For Part A of the study, patients with measurable and non-measurable disease can be recruited.	Efficacy
To determine inhibition of tumour glucose uptake by assessment with FDG-PET (Part A only).	Tumour averaged SUVmax (site and central review) Metabolic response rate at day 4 of multiple dosing and end of cycle 1 (percentage of patients with >25% reduction in average SUVmax)	Efficacy
Exploratory**	**Exploratory****	
Optional samples for Biomarker analysis research (Part A)		
To evaluate phosphorylation levels of S6 in buccal biopsies following treatment with AZD8055	Change in phosphorylation of the biomarker S6 in optional buccal biopsies.	Biomarkers
Optional host genetic research		
To investigate whether variability in the PK, safety, efficacy or PD results could be explained by differences in genetic variation (host genetic research)	Collection of a blood sample (optional) for DNA extraction and storage.	Pharmaco-genetics
Residual samples for Biomarker analysis research		
To explore potential biomarkers in residual biopsies, plasma and/or serum which may influence development of cancer and associated clinical characteristics and/or response to AZD8055	Correlation of biomarkers to response and/or development of cancer (such as but not limited to PTEN loss and PI3K mutation)	Biomarkers

AUC: Area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-12)}$: Area under plasma concentration-time curve from time zero to 12 hours post dose; $AUC_{(0-t)}$: Area under plasma concentration-time curve from time zero to time t; AUC_{ss}: Area under plasma concentration-time curve at steady-state; CL/F: Total apparent drug clearance CL_{ss}/F: Total apparent drug clearance at steady state; C_{max}: Maximum plasma concentration; $C_{max\ ss}$: Maximum (peak) steady state drug concentration in plasma during dosing

interval; C_{min}: Minimum plasma concentration; $C_{min\ ss}$: Minimum (trough) steady state drug concentration in plasma during dosing interval; CTCAE: Common Terminology Criteria Adverse Event; ECG: Electrocardiogram; FDG-PET: 2-[F-18]-fluoro-2-deoxy-D-glucose positron emission tomography; PBMC: Peripheral blood mononuclear cell; PD: Pharmacodynamics; PI3K Phosphatidylinositol 3 kinase; PK: Pharmacokinetics; PTEN: Phosphatase & Tensin homologue on Chromosome 10; RECIST: Response evaluation criteria in solid tumours; SUVmax: Maximum standardised uptake value; $t_{½}$: Half life; t_{max}: Time to reach maximum plasma concentration; $t_{max\ ss}$: Time to reach peak or maximum concentration at steady state; V_{ss}/F: Steady-state volume of distribution.

* PK/PD relationships were not analysed.

** Exploratory objectives results are not reported in the CSR synopsis.

Study design

This single ascending dose/multiple ascending dose study was designed to determine the tolerability profile and pharmacokinetics of AZD8055 in patients with advanced solid malignancies or lymphomas. It was a multi-centre, open label, dose escalation study aimed at defining the maximum tolerated dose (MTD) of AZD8055 after repeated dosing.

At the study outset, the clinical study protocol included Part A (dose escalation phase, to define the MTD) and Part B (expansion at the MTD, to further ascertain the compound safety profile, pharmacokinetics and provide preliminary efficacy information). Upon completion of recruitment into Part A it was decided that the characteristics of twice daily dosing of AZD8055 (safety, tolerability, PK, PK-PD) had been adequately assessed by Part A and therefore Part B was removed from the study design via a protocol amendment.

Cohorts of 3, 6 or more patients received a single dose of AZD8055 on Day 1 followed one week later by multiple twice daily dosing for 28 days (Cycle 1). After each dose cohort, the Safety Review Committee (SRC) evaluated the safety and tolerability of AZD8055 and decided the dose level for the next cohort. The starting dose for the first cohort was 10 mg. The first 2 cohorts recruited only three patients to minimise exposure to potentially sub-therapeutic levels of AZD8055.

Target subject population and sample size

Adult male and non-pregnant female patients with advanced solid malignancies or lymphomas, refractory to standard therapies or for which no standard therapies existed, or for which the investigator felt no other active therapy was required for the duration of the study, were eligible for enrolment into this study (patients required a World Health Organisation performance status of 0-2).

A dose was considered to be non-tolerated if ≥2/6 evaluable patients experience a Dose Limiting Toxicity (DLT). If cohorts 1 or 2 contained only 3 patients, then the dose would be considered to be non-tolerated if ≥2/3 evaluable patients experienced a DLT. When a non-tolerated dose was defined, dose escalations were stopped. An intermediate dose (ie one between the non-tolerated dose and the last dose tested before the non-tolerated dose) was allowed and could be assessed to determine the MTD. The MTD was defined as the last dose tested below the non-tolerated dose.

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

AZD8055 was administered initially in a liquid formulation to early cohorts. Following the 40 mg cohort (cohort 3), a tablet version of AZD8055 became available and the study switched to use this formulation for subsequent cohorts (from cohort 3a onwards). In total, seven cohorts were completed: solution at 10 mg, 20 mg and 40 mg and tablet at 40 mg, 60 mg, 90 mg and 120 mg twice daily (after the initial single dose on Day 1).

AZD8055 as a liquid formulation for oral use was supplied at 1 mg/mL and 10 mg/mL. AZD8055 tablet formulation was supplied in 10 mg, 20 mg and 100 mg strengths.

Seven different batches of the solution formulation of AZD8055 were used by patients during the course of the study [batch numbers P7460, P7461, P7462, P7597, P7598, P7599 and P7600] and three batches of AZD8055 tablet formulation were used [batch numbers F13687, F13689 and F13691].

Duration of treatment

The initial treatment of a single dose of AZD8055 was followed one week later by continuous twice daily dosing for 28 days (a total of 35 days for cycle 1). Subsequent cycles were 28 days in length. Patients were allowed to continue to receive AZD8055 as long as they continued to derive benefit from treatment, until disease progression (without further clinical benefit) or until they experienced unmanageable drug related toxicity.

Statistical methods

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

Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities Version 13.1. For all safety assessments (e.g. laboratory assessments, vital signs), the baseline value was defined as the last available measurement prior to the first dose of AZD8055.

Subject population

In total, 64 patients were enrolled into the study (informed consent received) at 4 study centres in 3 countries, of which 49 patients received at least 1 dose of study treatment.

Of the 49 dosed patients, 42 patients received at least 75% of the specified dose during the continuous 28-day dosing period of Cycle 1 and thus met the protocol definition of an evaluable patient. 35 of 49 dosed patients reached the Cycle 2 Day 8 visit (35 days of continuous dosing)

The most common reason for discontinuation of treatment (32 patients) was disease progression (measurable as per RECIST v1.0), with subjective disease progression the second most common reason (10 patients). See Table S2 (Summary of patient disposition) for full details of reasons for discontinuation of treatment with AZD8055.

Of 49 dosed patients, no patients were excluded from the safety, PK or efficacy analysis sets.

Table S1 Summary of patient disposition

		Reason for discontinuation of treatment			
Dose (twice daily)	**Total no. patients dosed**	**AE**	**Objective disease progression**	**Subjective disease progression**	**Voluntary (consent withdrawn)**
10 mg (s)	5	0	4	1	0
20 mg (s)	3	0	3	0	0
40 mg (s)	6	0	5	0	1
40 mg (t)	7	0	7	0	0
60 mg (t)	7	0	3	3	1
90 mg (t)	11	1	6	3	1
120 mg (t)	10	2	4	3	1
	49	**3**	**32**	**10**	**4**

s = solution formulation; t = tablet formulation

The demographic and baseline characteristics of the cohorts were generally comparable. The overall median age of patients at baseline was 57 years, with a majority of patients (75.5%) aged from 18-65 years. The primary tumour site varied but the most commonly reported sites were colorectal (16 patients, 32.7%) and uterus (6 patients, 12.2%). Medical and surgical history, physical examination findings and previous cancer therapies were as expected for a population of patients with advanced cancer.

Summary of efficacy results

No complete or partial responses (RECIST v1.0) were observed for any patient during the study.

Summary of pharmacokinetic results

Following the initial single dose of AZD8055, at dose levels from 10 mg to 120 mg across the cohorts, AZD8055 was found to be orally bioavailable, rapidly absorbed and with a mean terminal plasma elimination half-life of approximately 2-3 hours. AZD8055 demonstrated approximately proportional increases in exposure with increasing dose over the dose range investigated (following the single dose), although the variability within cohorts was high and exposures overlapped across different dose groups.

Following twice daily multiple doses of 10 mg to 120 mg, AZD8055 was again found to be orally bioavailable, rapidly absorbed and to have a mean terminal plasma elimination half-life of approximately 2 to 3 hours. An approximately proportional increase in exposure with increasing dose was seen for the solution formulation over the dose range of 10 mg to 40 mg

and a greater than proportional increases with increasing dose was seen for the tablet formulation over the dose range of 40 mg to 120 mg, with high variability within cohorts. After twice daily multiple dosing, a greater than expected accumulation was observed in some individuals and data also showed time dependent kinetics from single dose to steady state in some individuals.

The PK after administration of a 40 mg dose of either a solution or a tablet formulation are similar except for a short delay in time to peak as may be anticipated from a solid dosage form.

AZD8055 was observed to have low renal clearance, with less than 0.25% of the dose of AZD8055 being excreted unchanged in the urine at all dose levels in the first 24 hours following the single dose.

Summary of pharmacodynamic results

Analysis of FDG-PET data shows metabolic responses at doses of 40 mg and above.

Analysis of PBMC data demonstrated a transient decrease in p4EBP1 in 2/5 patients at 90 mg at 2 hours post-dose, however it should be noted that there was variability in pre-dose levels of the marker, and the overall number of patients' data presented is small.

A decrease in pAKT at 2 hours is noted in all patients in the 90 mg cohort with a baseline value > 5% (with very low pre-dose levels seen in the majority of patients). 8 out of 10 had baseline values < 15% and 4/10 had baseline values < 5% (Lower limit of quantification). In summary, a transient reduction in pAKT was seen in 6/10 patients at 2 hours post-dose, however the baseline variability and low sample number should also be noted.

A local protocol amendment applicable at one investigator site elicited the collection of matched pre and post-dose tumour biopsies for biomarker analysis. Two patients had a baseline and a post-dose tumour sample collected, the analysis of which did not show conclusive evidence of biomarker modulation.

Summary of pharmacokinetic/pharmacodynamic relationships

Pharmacokinetic and pharmacodynamic relationships were not analysed.

Summary of pharmacogenetic results

No analysis has been performed of pharmacogenetic data at the time of writing this synopsis.

Summary of safety results

Adverse events reported in the 49 patients exposed to AZD8055 were in keeping with an oncology Phase I study population. The most frequently reported adverse events across all cohorts (regardless of causality) were fatigue (55%), nausea (35%), decreased appetite (33%), diarrhoea (31%), constipation (27%), dyspnea exertional (22%) and vomiting (22%). Adverse

effects, which were considered to be not tolerated at the dose level of 120 mg twice daily were increased serum transaminases.

AZD8055 reached a non-tolerated dose of 120 mg twice daily in cohort 5. Side effects, which were considered not to be tolerated at this dose level were increases in liver function tests (transaminitis without Hy's law cases as defined per FDA DILI guidelines) in 3/10 patients (30%) in the 120 mg cohort.

13 out of 49 patients (26.5%) had a rise in transaminases of either a 2 grade shift from baseline and/or an on-treatment value of CTC grade 3. For 11 of these patients, transaminases (alanine aminotransferase (ALT) and or aspartate aminotranferase (AST)) were reported as an AE considered to be related to AZD8055 by the investigator. Of the 13 patients, 5 had liver metastases and 4 of them experienced liver disease progression as confounding factors. Increased liver function test results in one patient was considered by the investigator to be due to progression of disease rather than related to AZD8055. For the remaining 8 patients with no liver metastases, liver function test result increases were considered by the investigator to be possibly related to AZD8055.

20 patients experienced no grade shift changes to AST or ALT.

There were no cases of Hy's law (as defined per FDA DILI guidelines) identified in those patients who had a rise in liver enzymes or peak in liver enzymes during treatment with AZD8055.

In the 13 patients with rises in transaminitis (the rise was not acute), the rise occurred between days 1-56 of multiple dosing and generally between days 22-35 (for 7 of the 13 patients). The rises were manageable, reversible and generally resolved back to baseline or normal values in the majority of cases when the drug was stopped or dose reduced.

8 of 49 (16%) patients experienced at least one serious adverse event (SAE), the most common being transaminase increases (3 patients). Four deaths occurred (1 death of unknown cause and 3 due to disease progression).

Exposure data of AZD8055 showed 3 of 49 (6%) patients had a dose reduction due to an AE, with 12 of 49 (24.5%) patients having a dose interruption due to an AE. Transaminitis usually required dose interruptions.