Clinical Study Report Synopsis

Drug Substance	AZD8055
Study Code	D1600C00003
Edition Number	1
Date	30 November 2011

A Phase I, open label, single-centre study to assess the safety and tolerability of the Tor Kinase Inhibitor AZD8055 administered orally to Japanese patients with advanced solid tumours

Study dates: First subject enrolled: 18 August 2009
Last subject last visit: 21 December 2010

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

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	Type
Primary	**Primary**	
To assess the safety and tolerability of AZD8055 in Japanese patients with advanced solid tumours	Adverse events, clinical laboratory tests (clinical chemistry, haematology, coagulation, urinalysis), glucose management (s-glucose, s-insulin, haemoglobin A1c [HbA1c]), vital signs (pulse rate, blood pressure, weight and body temperature), ECG, echocardiography (including Doppler measurements), lung CT, nervous and musculoskeletal system examination	Safety
Secondary	**Secondary**	
To determine the pharmacokinetics of AZD8055 following both single and multiple oral dosing of AZD8055 in patients with advanced solid tumours	Where the data allow, single dose and multiple dose PK parameters will be calculated: Single dose: C_{max}, t_{max}, $t_{½}$, AUC, AUC_{0-t}, AUC_{0-12}, AUC_{0-24},CL/F, V_{ss}/F, Ae, fe and CL_R/F Multiple dose: C_{min} samples during escalation to steady state, at steady state $C_{max\ ss}$, $t_{max\ ss}$, $C_{min\ ss}$, $t_{½}$, AUC_{ss}, CL_{ss}/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 seek preliminary evidence of the anti-tumour activity of AZD8055 in patients with advanced solid malignancies	Objective tumour response (according to modified RECIST criteria)	Efficacy

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Exploratory		
To determine phosphorylation levels of downstream markers in the PI3K/AKT/mTOR pathway following treatment with AZD8055	pAKT, p4E-BP1	PD (Biomarker)
To evaluate relationships between exploratory biomarkers in blood samples	Not applicable *	PD

Ae: Amount of unchanged drug excreted into urine; AUC: Area under the plasma concentration-time curve from zero to infinity; AUC_{0-12}: Area under the plasma concentration-time curve from zero to 12 hours post dose; AUC_{0-24}: Area under the plasma concentration-time curve from zero to 24 hours post dose; AUC_{0-t}: Area under the plasma concentration-time curve from zero to time of the last quantifiable concentration; AUC_{ss}: Area under the plasma concentration-time curve interval at steady state; C_{max}: Maximum plasma drug concentration; CL/F: Total apparent drug clearance; CL_R: Renal clearance; CL_{ss}/F: Total apparent drug clearance at steady state; $C_{max\ ss}$: Maximum (peak) steady state drug concentration in plasma during dosing interval; $C_{min\ ss}$: Minimum (trough) steady state drug concentration in plasma during dosing interval; CT: Computed Tomography; ECG: Electrocardiogram; fe: Fraction excreted unchanged in urine; p4E-BP1: eukaryotic initiation factor eIF4E binding protein; pAKT: Protein kinase B; PK: Pharmacokinetics; RECIST: Response evaluation criteria in solid tumours; t_{max}: Time to reach maximum plasma concentration; $t_{max\ ss}$: Time to reach maximum plasma concentration at steady state; $t_{1/2}$: Half life, V_{ss}/F: Steady-state volume of distribution

* These results are not reported in the CSR synopsis. When the results will be available, the separate report will be prepared.

Study design

This was a Phase I, open-label, dose-escalation study. The study was designed to assess safety, tolerability, and pharmacokinetic profiles of AZD8055 in Japanese patients with advanced solid tumours. There was a minimum of 3 and a maximum of 6 evaluable patients per cohort at each dose level.

Target subject population and sample size

Adult patients with histologically or cytologically confirmed solid malignancy that had progressed despite standard therapy or for whom no standard therapy exists were enrolled into the study.

A minimum of 3 and maximum of 6 patients were enrolled into each dose level.

The sample size was determined based on the policy of obtaining the safety and PK data in a minimum number of patients at each dose with the primary objective of investigating drug adverse effects in accordance with the "Guideline for Clinical Evaluation of Anti-Malignant Tumor Agents (PFSB/ELD Notification No. 1101001 dated 1 November 2005)" that is applied to Phase I studies of anticancer drugs in Japan.

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

AZD8055 was administered orally in the morning in Day 1 and in the morning and evening (twice daily) in Day 3 and after. The dose interval was approximately 12 hours at Day 3 and after in the fasting condition. The patient refrained from eating for at least 2 hours pre-dose and 1 hour post-dose (only water was permitted). In the case of vomiting after taking a tablet and incompliance re-dosing should not be performed. The starting dose of AZD8055 was "10 mg single dose in the morning in Day 1 and 10 mg twice daily in the morning and evening in Day 3 and after". The maximum dose in this study was to be a non-tolerated dose (1 dose level higher than the maximum tolerated dose [MTD]) or the MTD defined in the western Phase I study.

Cycles nominally lasted for 28 days (except for Cycle 1 for 30 days: single dose at Day 1, one day's wash-out at Day 2, followed by 28 days multiple dosing period from Day 3 to Day 30).

Duration of treatment

For the purposes of the protocol, cycles were nominally last for 28 days (except for Cycle 1 for 30 days: single dose at Day 1, one day's wash-out at Day 2, followed by 28 days multiple dosing period form Day 3 to Day 30). Patients continuing to tolerate the treatment without dose-limiting toxicities repeated this schedule until no clinical benefit was apparent (ie, patient has progressive disease), or the patient was withdrawn for other reasons.

Statistical methods

No formal statistical analysis was performed. Safety and PK data were listed and summarised by use of descriptive statistics. Graphical presentations of the data were produced to aid interpretation.

Subject population

A total of 19 patients were enrolled into the study, of whom, 17 patients received at least 1 dose of study medication (3 patients in 10 mg bid cohort, 4 patients in 40 mg bid cohort, 3 patients in 60 mg bid cohort, and 7 patients in 90 mg bid cohort).

Of the 17 dosed patients, 15 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 for dose limiting toxicity (DLT).

The reasons for treatment discontinuation were disease progression (10 patients), lost to follow-up (3 patients), voluntary discontinuation (2 patients), adverse events (1 patient) and death due to disease progression (1 patient).

In total, 17 patients who received at least 1 dose of study medication were included in the efficacy analysis set, PK analysis set, Pharmacodynamic (biomarker) analysis set, and safety analysis set.

The overall demographic and baseline characteristics were representative of the intended population. The median age of patients at baseline was 52 years (range: 35 – 76 years), with a majority of patients (88.2%) aged from 20-65 years. A total of 11 patients (64.7%) were female, and 6 and 11 patients were Performance status 0 and 1, respectively. The primary tumour site was skin/soft tissue in 12 patients, lung and pancreas in 2 patients respectively, and breast in 1 patient. All patients had metastatic lesion(s) and the majority patients had received previous chemotherapy (14/17 Patient, 82.4%).

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 90 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 hours. AZD8055 demonstrated slightly more than proportional increases in exposure with increasing dose over the dose range investigated (following the single dose), although the number of subjects was limited and the variability within cohorts was high and exposures overlapped across different dose groups.

Following twice daily multiple doses of 10 mg to 90 mg, AZD8055 was again found to be orally bioavailable, rapidly absorbed and to have a mean terminal plasma elimination half-life of approximately 2 hours. More than proportional increases in exposure with increasing dose was seen over the dose range of 10 mg to 90 mg with high variability in limited number of patients 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.

AZD8055 was observed to have low renal clearance, with less than 0.14% 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

Pharmacological effects in mTOR inhibition was suggested to be achieved based on decreased pAKT/p4E-BP1 activity in peripheral blood mononuclear cells (PBMCs) at doses which were investigated in the study (10 mg bid to 90 mg bid). 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.

The pAKT level decreased to reach the maximum level 2 hours post the single dose of AZD8055 at all dose cohort level followed by gradually recovered to the baseline level. p4E-BP1 level decreased to reach the maximum level reached 2 hours at cohort of 10 mg, 60 mg and 90 mg bid post the single dose of AZD8055 followed by recovered quickly to the baseline level at 8 hours post dosing.

Summary of safety results

Adverse events were reported in the 16/17 patients (94.1%) exposed to AZD8055. The most frequently reported adverse events across all cohorts (regardless of causality) were stomatitis (10/17 patients), rash (6/17 patients), decreased appetite (6/17 patients), nausea (5/17 patients), alanine aminotransferase (ALT) increased (5/17 pts), and aspartate aminotransferase (AST) increased (5/17 patients). Most AEs were grade 1 or 2 except for ALT increased and AST increased. Two of five in ALT increased and one of five in AST increased were CTC grade 3.

Across all cohorts, one patient experienced the DLT (AST increased and ALT increased) out of 6 patients evaluable for DLT assessment in 90 mg bid cohort, therefore, up to 90 mg bid is identified as tolerable dose for Japanese patients in this study.

4 of 17 patients in 90 mg bid cohort experienced at least one serious adverse event (SAE). All SAEs were liver function related events. One patient died due to disease progression and no patient died due to AE. One patient discontinued study treatment due to AE in 90 mg bid cohort (the patient is also a SAE case).

Median exposure period was 30 days (range: 24-89 days) in 10 mg bid cohort, 29.5 days (14-60 days) in 40 mg bid cohort, 30 days (30-60 days) in 60 mg bid cohort, and 30 days (13-88 days) in 90 mg bid cohort. No dose reduction/interruption were reported.

9 of 17 patients had a rise in liver function test (LFT) (developing of CTCAE grade 1 or higher value during the treatment period). Geometric mean exposures of AZD8055 are higher in patients with LFT increase than those without LFT increase. There are patients with equally high exposures who do not show any LFT changes so it is not just a function of the systemic exposure.

No treatment-emergent changes were observed for other laboratory, vital signs, or ECG data, with the exception of liver function findings observed as AEs, ALT and AST increased.