AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8055
Study Code	D1600C00014
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A Phase I/II, Open-label, Multicentre Study to Assess the Safety & Tolerability, and Pharmacokinetics of AZD8055 in Asian Patients with Advanced Stage Hepatocellular Carcinoma (HCC) and with Mild or Moderate Hepatic Impairment

Study dates: First subject enrolled: 26 October 2009
Last subject last visit: 01 December 2011

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 3 centres, in Hong Kong and Korea.

Publications

None at the time of writing this synopsis.

Objectives and criteria for evaluation

Table S 1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To evaluate the safety/tolerability of AZD8055 in advanced stage HCC subjects with Child Pugh A and B status (see Appendix I), including determination of the MTD.	Incidence and severity of adverse events (CTCAE Version 3.0), vital signs, ECG and echocardiography, clinical chemistry, haematology and urinalysis, physical examination and pulmonary function test.
Secondary	PK	To determine the pharmacokinetics of AZD8055 following both single and multiple oral dosing of AZD8055 in patients with advanced stage HCC subjects with Child Pugh A and B status.	Where the data allow, single dose and multiple dose pharmacokinetic parameters will be calculated, which may include but not be restricted to: • single dose: C_{max}, t_{max}, $t_{1/2}$, AUC, AUC_{0-t}, AUC_{0-12}, CL/F and V_{ss}/F • multiple dose: Cmin samples during escalation to steady state, at steady state Cmax ss, tmax ss, Cmin ss, $t_{1/2}$, AUCss, CLss/F, and accumulation ratio
	PK	To determine the extent of renal excretion in the disposition of AZD8055 in this population	Amount of AZD8055 excreted unchanged in the urine (Ae) in the period immediately following dosing, percentage dose excreted (fe %) and renal clearance (CL_R)

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	Biomarkers	To evaluate phosphorylation levels of biomarkers such as, but not limited to, AKT following treatment with AZD8055	Change in phosphorylation of biomarkers such as, but not limited to AKT in PBMCs (isolated from blood samples). (All residual biomarker samples may be investigated for other cancer related biomarkers).
	Efficacy	To make a preliminary assessment of antitumour activity by evaluation of tumour size	Objective Response Rate, Best Overall Response, percent change from baseline in tumour size measured at the end of Cycle 1 (based on RECIST) for patients with measurable disease
	Efficacy	To evaluate the biochemical response in serum alpha fetoprotein (AFP) to AZD8055 (in the dose escalation phase)	Serum AFP level
	Efficacy	To evaluate hepatitis virus replication under AZD8055	Virology indicating hepatitis virus replication by PCR assay: • Changes from baseline in HBV DNA replication • Changes from baseline in HCV RNA replication
	Efficacy	To evaluate potential immunosuppression by AZD8055	WBC counts and differential, lymphocyte count and subset phenotyping
	PK/PD*	To investigate possible relationships between plasma AZD8055 concentrations/exposure and liver impairment.	Where data permit, the PK (AZD8055 exposure)/liver impairment relationship will be explored by using appropriate modelling techniques

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory **	Biomarkers	Optional samples for Biomarker analysis: To investigate the effect of AZD8055 on the inhibition of AKT and 4E-BP1 phosphorylation in optional matched pre- and post-dose tumour biopsies	Paired tumour biopsies - Baseline and change from baseline in biomarkers related to mTOR activity (for example phosphorylation of AKT and 4E-BP1) and other cancer related biomarkers (such as but not exclusively PTEN loss and PI3K mutation/amplification) in matched pre- and post- dose tumour biopsies.
		To assess markers of pathway activation such as, but not limited to PTEN and PI3K which may have been acquired since diagnostic of the disease and may impact of the activity of AZD8055	Archival tumour - Measurement of markers of pathway activation such as, but not limited to PTEN and PI3K in diagnostic samples and study biopsies
	Pharmacogenetics	Optional pharmacogenetics research: To collect and store DNA for future exploratory research into genes that may influence response to AZD8055 (e.g. distribution, safety, tolerability and efficacy) and/or susceptibility to cancer	Correlation of genetic polymorphisms with variation in response (e.g. distribution, safety, tolerability and efficacy) and/or susceptibility to cancer

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; PBMC: Peripheral blood mononuclear cell; PI3K: Phosphatidylinositol 3 kinase; PK: Pharmacokinetics; PTEN: Phosphatase & Tensin homologue on Chromosome 10; RECIST: Response evaluation criteria in solid tumours; $t_{½}$: 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 is an open-label, single ascending dose/multiple ascending dose study in patients with advanced stage HCC. This study procedure will be followed in Child Pugh A and B groups, respectively.

The study will be conducted with different cohorts for either Child Pugh A or Child Pugh B patients, to allow appropriate dose escalation steps as a consequence of disease burden, different safety and pharmacokinetic parameters. Accordingly patients with Child Pugh A or Child Pugh B will be dosed sequentially (appendix J), starting with Child Pugh A patients. Both Child Pugh A and B groups (cohort 1 A and B) will be treated with the same starting dose.

Cohorts comprising a minimum of 3 evaluable patients and a maximum of 6 evaluable patients will receive a single dose of AZD8055 followed 2 days later (Day 3) by multiple twice daily dosing for 28 days (Day 3-30). Each subsequent cohort will receive an increased dose, assuming the previous dose was well tolerated, until a non-tolerated dose is reached. The number of cohorts will be dependent on the tolerability of the compound. At the end of 28 days multiple dosing patients may continue to receive AZD8055 at the discretion of the investigator until disease progression or until they experience unmanageable drug related toxicity, as long as they are continuing to derive clinical benefit. In the absence of significant toxicity patients will be permitted to continue to receive AZD8055 after objective disease progression if in the opinion of the investigator, they are continuing to derive clinical benefit.

Target subject population and sample size

There is no formal sample sizing for this study. This is a standard Phase I/II design in which the number of patients enrolled will be sufficient to be confident of tolerability whilst minimising exposure to testing drug.

Adult male and non-pregnant female patients with advanced stage HCC and with liver function classified as either Child Pugh A or B, whose tumour was not resectable or incurable by ablative therapy or transarterial chemoembolization (TACE) and with no standard therapy available, were entered into the study.

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. On Day 1 (single dosing) the drug was taken on a fasted stomach as early as possible during this day. During the multiple dose period (day 3-30 and thereafter) doses were taken on a fasted stomach at approximately the same time each morning and evening approximately 12 hours apart. Patients refrained from eating (water to drink only) for ≥ 2 hours prior to taking a dose to ≥ 1 hour post-dose. If a patient missed any dose either through poor compliance or, for example, due to vomiting, this dose was not made up and the patient was asked to take the next scheduled dose.

In total, three cohorts in Child-Pugh A patients were tested: 10mg, 20mg and 40mg. One cohort with 10mg was tested in Child-Pugh B patients

Four batches of AZD8055 tablet formulation were used [F13687, F13805, F13689, F13779].

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 from 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 for the primary objective of this study. Data were listed and summarised. Graphical presentations of the data were produced to aid interpretation.

Subject population

A total of 23 patients were enrolled into the study, of whom, 17 patients received at least 1 dose of study medication (Child Pugh A: 9 patients in 10mg bid cohort(enrolled additional patients to have sufficient safety data before Child Pugh B cohort), 3 patients in 20mg bid cohort, 3 patients in 40mg bid cohort; Child Pugh B: 2 patients in 10mg bid cohort).

Of the 17 dosed patients, 17 patients (100%) 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 discontinuation were objective disease progression (13 patients), development of Study Specific Discontinuation Criteria (3 patients) and adverse events (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 set.

The overall demographic and baseline characteristics were representative of the intended population. The median age of patients at baseline was 58 years (ranges: 41-71 years), with a majority of patients (88.2%) aged from 18-65 years. A total of 12 patients (70.6%) were male, and 14 and 3 patients were Performance status 0 and 1, respectively. The primary tumour site was liver for all the patients. All patients had metastatic lesion(s) and the majority patients had received previous chemotherapy (16/17, 94.1%).

Summary of efficacy results

No complete or partial responses were observed for any patient during the study, based on a count of the investigator opinion of response. Of 17 dosed patients, 6 patients showed stable disease (35.3%).

No significant change due to AZD8055 was identified in AFP.

Summary of pharmacokinetic results

Following both the initial single dose and twice daily multiple dosing, AZD8055, administered as a tablet formulation at dose levels from 10 mg to 40 mg, was found to be orally bioavailable, rapidly absorbed and have a mean terminal plasma elimination half-life of approximately 2-3 hours. AZD8055 demonstrated a slightly less than proportional increase in exposure with increasing dose in the mildly hepatically impaired (CPA) patients over the dose range investigated (4-fold increase in dose from 10mg to 40mg giving only an approximately 2.5-fold increase in AUC), although patient numbers were small, variability within cohorts was high and exposures overlapped across the different dose groups.

After twice daily multiple dosing there was on average little evidence of accumulation and the single dose kinetics were largely predictive of the steady state PK, although again this is based on data from small patient numbers with high inter-patient variability.

PK data for the CPB 10mg cohort, available for two patients following a single dose and for one patient following multiple dosing, suggested that exposure may be higher in these moderately hepatically impaired patients than that at the same 10mg dose in the mildly hepatically impaired CPA patients.

When compared to data from Study 1 (Western patients) and Study 3 (Japanese patients) the exposure (Cmax and AUC) for Asian CPA and CPB patients appeared to be higher after both single and multiple doses. Mean exposures after 40mg BD dosing to CPA patients were higher than mean exposures for the 90mg BD dose declared to be the MTD in the Western population in Study 1.

No urine PK data were available for reporting.

Summary of pharmacodynamic results

Pharmacodynamic results were not analysed.

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 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 decreased appetite (4/17 patients), upper respiratory tract infection (3/17 patients), aspartate aminotransferase (AST) increased (3/17 patients), blood bilirubin increased (3/17 patients), nausea (3/17 patients), oedema peripheral (3/17 patients), cough (3/17 patients), back pain (3/17 patients) and hypertension (3/17 patients).Most AEs were grade 1 or 2 except for AST increased, bilirubin increased and hypertension.

Across all cohorts, no patient experienced the DLT in this phase I study. The highest dose tested in this study was 40mg which showed a higher $_g$mean level in both C_{max} and AUC than 90mg cohort in western patients. 90mg was announced as MTD in the study with western patients. Therefore, treatment was stopped at this dose level although 40mg Bid was well tolerated. in these Asian patients with mild hepatic impairment HCC. Only 2 patients with moderate hepatic impairment advanced HCC (CPB) in this study were dosed with 10mg Bid with no DLT found.

35.3% (6/17) patients had SAEs, all in Child-Pugh A arm with 4 patients in 10mg cohort (ascites, cerebellar infarction, fever, shoulder pain), 1 in 20mg in cohort (Death due to traffic accident) and 1 in 40mg cohort (Vocal cord hoarseness). None of the SAE was considered to be related to AZD8055 by investigators.

During the study, no dose adjustments or dose reductions were reported. 2/17 (11.8%) patients had a dose interruption due to and AE. One patient in Child-Pugh A 10mg cohort interrupted dose due to pneumonia and one patient in 20mg interrupted dose due to albuminuria. Two patients discontinued study treatment due to AE, both in 10mg cohort in Child-Pugh A patients.

Three out of 17 patients (17.6%) in study D1600C00014 reported ALT/AST rises as adverse events, with 2 CTC grade 1 adverse events and 1 CTC grade 3 adverse event. The two grade 1 ALT/AST adverse events were considered to be related to AZD8055 by the investigator.

No dose-limiting transaminitis was reported during the whole study.

Two patients in Child-Pugh A 10mg cohort reported Hepatitis B viral load increase.
E0001001 had a 4-fold increase in Hepatitis B viral load after 1 cycle of treatment, which aggravated to 54-fold after 3 cycles, and this increase was accompanied by grade 2/3 ALT/AST increase. However the AE (ALT/AST increase) was considered related to disease progression and not to be related to AZD8055.
E000 1003 had a 7-fold increase in Hepatitis B viral load after 2 cycles of treatment together with grade 1 ALT/AST increase, and the ALT/AST increase was considered to be possibly related to AZD8055.

Three deaths occurred, 1 death of cerebellar infarction, 1 death of car accident and 1 death of disease progression all unrelated to study drug.