AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6918
Study Code	D2785C00002
Edition Number	1
Date	16 June 2009

A Phase I, Open-Label, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD6918 Administered Daily as a Single Agent and in Combination Treatment in Adult Patients with Refractory Solid Malignancies

Study dates: First patient enrolled: 6 August 2008
Last patient completed: 12 March 2009

Phase of development: Clinical pharmacology (I)

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

Study center(s)

This study was conducted at 2 study sites in the United States:

Publications

None at the time of writing this report.

Early termination of study

Study D2785C00002 was a Phase 1 study to evaluate the safety, tolerability and pharmacokinetics of an oral formulation of AZD6918 alone and in combination with either gemcitabine or pemetrexed in 2 separate arms. The first patient was enrolled on 6 August 2008, and the last patient completed the study on 12 March 2009. A decision to prematurely terminate the study was taken on 9 Feb 2009 and communicated to investigators. The reason for premature termination of the study was that the observed PK profile of AZD6918 in cancer patients showed that exposure was extremely low, as indicated by a lower C_{max}, C_{min}, and AUC, and that the apparent clearance was higher than predicted from animal studies. Based on this profile, as well as the variability observed among patients in the highest dose cohort (80 mg), the only cohort that included more than 1 patient, it was judged unlikely that an efficacious dose of AZD6918 could be reached. No safety issues were identified.

Objectives

The primary objective of this study was to identify a pharmacokinetically (PK)-guided estimated biologically effective dose (eBED) and maximum tolerated dose (MTD).

The secondary objectives were:

- To evaluate the safety and tolerability of AZD6918 as a single agent
- To evaluate the safety and tolerability of AZD6918 given in combination with chemotherapy (either pemetrexed or gemcitabine)
- To determine the pharmacokinetic profile of AZD6918 following single and multiple dose administration
- To evaluate the pharmacokinetics of AZD6918 and the selected chemotherapy agents when given in combination to determine if pharmacokinetics are altered by co-administration

The exploratory objectives were:

- To seek preliminary evidence of the anti-tumor activity of AZD6918
- To correlate tumor biologic characteristics and clinical outcome using archival tumor tissue. All patients were required to consent although archival tissue did not have to be available at time of therapy initiation and was not a requirement for evaluability (samples were collected but have not been analyzed and are not presented in this Synopsis).

Optional: To obtain a blood sample for deoxyribonucleic acid (DNA) extraction for retrospective pharmacogenetic analysis (samples were collected but have not been analyzed and are not presented in this Synopsis).

Optional: Surplus blood or tissue samples may be analyzed for exploratory biomarkers to evaluate relationships between cancer related biomarkers and study treatments as part of a larger effort of biomarker evaluation (samples were collected but have not been analyzed and are not presented in this Synopsis).

Study design

Study D2785C00002 was a Phase 1, open-label, multi-center study to assess the safety, tolerability and pharmacokinetics of an oral formulation of AZD6918 (an inhibitor of tropomyosin-related kinase [Trk] receptors). The study was designed to include 2 parts, with each patient participating in only 1 part:

- **Part A** (Dose Escalation Phase) was designed to identify the safety, tolerability and PK of daily oral AZD6918 as a single agent up to eBED and MTD.
- In **Part B** (Combination Expansion Phase), the eBED of AZD6918, if <MTD, (possibly MTD also, if significantly greater than eBED) was to be combined with gemcitabine or pemetrexed in 2 separate arms. Two dose levels of each chemotherapy were to be tested, and the highest dose at which <2/6 evaluable patients experienced dose-limiting toxicities (DLT) would be considered the MTD. Hence Part B was designed to assess safety and additional PK data of combination therapy.

No patients were enrolled in Part B of this study; therefore, the remainder of this Synopsis will address methods and results relating only to Part A.

During the Dose Escalation Phase, each dose cohort was to consist of 1 evaluable patient unless the patient experienced either of the following: 1) any CTCAE[1] Grade ≥2 non-disease

[1] Common Terminology Criteria Adverse Event, Version 3.0.

related adverse event (AE) in the first cycle, or 2) a steady-state minimum AZD6918 plasma concentration of ≥80 nM at 24 hours on Day 9; in these cases, a dose cohort was expanded to include 2 additional evaluable patients (ie, a minimum of 3 evaluable patients). Criteria for expanding a cohort beyond 3 patients were outlined in the Clinical Study Protocol; however, there were no cohorts that included more than 3 patients in this study.

The starting dose of 20 mg was based on margins established through pre-clinical mouse and dog toxicology data and estimate of the Minimum Anticipated Biological Effect Level (MABEL). This dose represented $1/60^{th}$ of the $1/10^{th}$ the severely toxic dose (STD_{10}) in mice, $1/15^{th}$ of the no-observed-adverse-effect-level (NOAEL) in dogs and was approximately equivalent to the MABEL for tumor effect in an engineered mouse model. Dose Escalation was to be 100% in 1-patient cohorts until non-disease related CTCAE Grade ≥2 occurred during the first cycle. Subsequent dose escalations were to be 50% or 25%.

Target patient population and sample size

The target population included patients ≥18 years with histologically confirmed solid malignancy that was recurrent, metastatic, and/or unresectable, and for which standard curative or palliative measures did not exist or were no longer effective. A total enrollment of approximately 75 patients was planned for Parts A and B.

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

AZD6918 was supplied as a suspension (10 mg/mL) and administered orally once daily on an empty stomach. It was administered in doses of 20, 40, or 80 mg for the patients treated in this study. The formulations and batch numbers for this open-label investigational product were as follows: 1) Formulation Number F013630, Batch Numbers 2000116836 and 2000117034, and 2) Formulation Number F013650, Batch Numbers 2000117036 and 2000117387.

Duration of treatment

For Cycle 1 only, patients were to receive 21 days of AZD6918, followed by a 1-week observation period. If the patient remained on study, all subsequent cycles were to consist of 28 days of AZD6918 as continuous, once-daily dosing. At the Investigator's discretion, individual patients could receive consecutive treatment cycles provided: (1) they were continuing to benefit, and (2) they did not meet any other withdrawal criteria. Patients were to be followed for safety up to 30 days after last administration of AZD6918.

Criteria for evaluation - pharmacokinetics and efficacy (main variables)

PK variables: *AZD6918 (single dose):* C_{max}, T_{max}, AUC, AUC $(_{0\text{-}24})$, AUC $_{(0\text{-}t),}$ CL/F, V_z/F, $t_{1/2}$ *AZD6918 (multiple dose):* $C_{max,ss,}$ $T_{max,ss,}$ $C_{min,ss,}$ $T_{min,ss,}$ $C_{avg,\ ss,}$ $AUC_{\tau,\ ss,}$ $AUC_{(0\text{-}t),}$ $CL_{ss}/F,$ $V_{ss}/F,$ $t_{1/2ss,}$ $R_{ac,}$ MRT.

Efficacy variables: investigator assessment of overall best response per RECIST; number of patients with stable disease >16 weeks.

Criteria for evaluation - safety (main variables)

Safety variables: CTCAE grade and type of AEs and DLTs; changes in laboratory values, vital signs (including weight), physical exams, and ECGs (heart rate, PR, R-R and QT intervals and QTc[Fridericia]).

Because of the non-clinical/preclinical signs of reversible ataxia, which might reflect potential neurological activity, this study incorporated clinical safety assessment using the Mini-Mental State Examination (MMSE©), and International Co-operative Ataxia Rating Scale (ICARS) to assess for ataxia/cerebellar dysfunction. However, these assessments were not to be used for clinical decision-making in isolation, as the tools have not been validated in the target patient population. Pain assessment was measured on the clinical 0-10 scale, and pain medication use was recorded. The Karnofsky Performance Scale was used to assess a patient's ability to carry out activities of daily living.

As a result of preclinical findings in dogs of transient, dose-related decreases in systemic blood pressure with compensatory increases in heart rate, supine and standing blood pressures and pulse rates were measured at each visit.

Statistical methods

No formal statistical analyses were planned for this study. Because only 1 of the 3 dose levels investigated included more than 1 patient, summary output has been limited to demographic variables, disposition, PK variables, DLTs, and overview of AEs. Patient listings are provided for all variables collected in the study. Summary output, figures, and patient listings are included in the Clinical Study Report.

Subject population

A total of 7 patients were enrolled in this study (ie, signed informed consent); 5 of these received at least 1 dose of AZD6918 and comprised the safety analysis set. One patient was assigned to the 20 mg starting dose cohort and remained on treatment for a total of 112 days (ie, four 28-day cycles). One patient was assigned to the 40 mg escalation cohort and remained on treatment for 42 days. The first patient assigned to the 80 mg escalation cohort experienced two Grade 3 DLTs that were assessed by the investigator as possibly drug-related (see Summary of Safety Results, below). As a result (and per protocol), 2 additional patients were included in the 80 mg cohort. Treatment duration in the 80 mg cohort ranged from 13 to 57 days.

The dosed patients had a mean age of 58.0 years (range: 47 to 71 years). All 5 dosed patients were White and 4 (80%) were women. All patients had metastatic disease, with primary tumor types of colon (1), skin/soft tissue (2), breast (1), and melanoma[2](1). Three of the

[2] In the study database, this patient's primary tumor was incorrectly coded as a CNS tumor; however, this patient had melanoma of unknown primary with metastatic deposits in the pituitary and liver.

dosed patients discontinued because "condition under investigation worsened;" the other 2 dosed patients discontinued due to adverse event(s) (DAE).

Summary of pharmacokinetic results

All 5 patients dosed orally with AZD6918 were evaluable for pharmacokinetics. Plasma concentrations of AZD6918 were below the lower limit of quantification (LOQ: 1 ng/mL) at the lowest dose of 20 mg.

At the 40 mg dose level (n=1), exposure of AZD6918 on Day 1 and Day 8 (steady-state) of dosing were low, with values at steady-state of 1.39 ng/mL for C_{max} and 1.46 ng*h/mL for $AUC_{0\text{-}tlast}$. Following dosing at 80 mg (n=3), AZD6918 was rapidly absorbed with a median $T_{max,ss}$ of 0.75 h (range: 0.50 to 0.78 h). Plasma $C_{max,ss}$ (44.3 ng/mL, CV 270%) and $AUC_{0\text{-}last,ss}$ (67.2 ng*h/mL, CV 251%) were approximately 32- and 46-fold higher, respectively, compared to the 40 mg dose, although considerable inter-subject variability was observed. The geometric mean (gmean) $C_{min,ss}$ was 1.11 ng/mL (CV 12%) and was well below the estimated plasma concentration (32 ng/mL) required for biological activity.

The estimated AZD6918 steady-state apparent volume of distribution appeared to be large (V_{ss}/F 7320 L; CV 34%) with an apparent clearance of 1136 L/h (CV 216%). Since the absolute bioavailability (F) is unknown, it is difficult to interpret these findings. Plasma concentrations declined rapidly from C_{max} up to 4 h postdose and then more slowly, with a mean $t_{1/2,ss}$ of 8.64 h (range: 1.51 to 13.0 h).

The observed pharmacokinetic profile is characterized by a multi-exponential decline, lower C_{max}, C_{min} and AUC, and apparently higher clearance than predicted from pre-clinical studies. Based on this pharmacokinetic profile and the variability observed among patients at the 80 mg dose, a very high dose was likely to be necessary to achieve the plasma concentration required for biological activity (estimated to be 32 ng/mL). Since most of the predicted doses were above the maximal absorbable dose, it was judged unlikely that an appropriate biologically efficacious dose (BED) of AZD6918 could be reached.

Summary of efficacy results

All 5 dosed patients had measurable disease at baseline. Of these, 4 had postbaseline tumor assessments performed. There were no complete or partial responses according to RECIST.

Summary of safety results

The MTD for AZD6918 was not identified in this study. All dosed patients had at least 1 AE. There were no neurological AEs. Two patients (D2785C00002/E0001001 and D2785C00002/E0001002) died due to disease progression and also, in the case of Patient D2785C00002/E0001001, to liver dysfunction. Both of these patients also experienced DAEs. Additional details of each of these 2 cases are provided below:

- Patient D2785C00002/E0001001 (female/65 years old/melanoma/80 mg cohort) experienced 2 DLTs (Grade 3 bilateral lower extremity edema and abdominal

edema); these were considered possibly related to study medication by the Investigator and by the AstraZeneca Study Team physician and Global Safety physician, and they resulted in discontinuation of study medication (DAEs). While these DLTs were not reported as SAEs by the Investigator and, therefore, do not appear as SAEs in the study database, the AstraZeneca Study Team physician and Global Safety physician considered the events to be medically important, and upgraded them to SAEs in the Global Safety database.

- Patient D2785C00002/E0001002 (female/47 years old/breast/80 mg cohort), who had liver metastases, experienced 4 DAEs, none considered related to study medication: Grade 3 elevated alkaline phosphatase, Grade 2 elevated AST and total bilirubin, and Grade 3 abdominal pain.

Although instances of acute, reversible decreases in systolic and/or diastolic blood pressure were recorded in some patients, interpretation of these results was confounded by concomitant anti-hypertensive medications in 3 of the 5 patients. ECG findings were unremarkable; there were no QT or QTc intervals >500 msec. Laboratory, vital signs, and physical exam data did not reveal any major safety concerns.