AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6244
Study Code	D1532C00005
Edition Number	1
Date	13 November 2008

A Phase I, Open-Label, Multi-centre Study to Assess the Safety, Tolerability and Pharmacokinetics of a Solid Oral Dosage Formulation (capsule) of AZD6244 in Patients with Advanced Solid Malignancies

Study dates: First patient enrolled: 8 March 2007
Last patient enrolled: 27 December 2007
Data cut-off data: 17 June 2008

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)

Four centres from the following 3 countries participated in this study: Netherlands (2), United Kingdom (1), United States (1).

Publications

Agarwal R, Banerji U, Camidge DR, Brown KH, Cantarini MV, Morris C et al. The first-in-human study of the solid oral dosage form of AZD6244 (ARRY-142886): A phase I trial in patients with advanced cancer. Abstract 3535, presented at ASCO Annual Meeting, Chicago USA, May 30-June 3 2008.

Sarker D, Banerji U, Agarwal R, Camidge DR, Verheul HMW, Brown KH et al. Relative oral bioavailability of the hydrogen sulphate (hyd-sulfate) capsule and free-base suspension formulations of AZD6244 (ARRY-142886): A phase I trial in patients with advanced cancer. Abstract 492P, presented at ESMO Congress, Stockholm, Sweden, 12-16 September 2008.

Objectives

Primary objective

- To assess the safety and tolerability of the capsule formulation of AZD6244 in patients with advanced solid malignancies

Secondary objectives

- To determine the pharmacokinetics (PK) of AZD6244 and N-desmethyl AZD6244 following both single and multiple oral dosing of AZD6244 capsule formulation in patients with advanced solid malignancies[1]
- To investigate possible relationships between plasma AZD6244 and/or N-desmethyl AZD6244 concentrations/exposure and changes in pharmacodynamic and safety parameters in patients with solid malignancies[2]
- Part B only: To determine the relative oral bioavailability of AZD6244 capsule formulation to the mix and drink formulation (100 mg), in patients with advanced solid malignancies

[1] The PK of the AZD6244 amide metabolite was also investigated, following assay development since the CSP was written

[2] This objective will be fulfilled at a later date, with data combined across the AZD6244 programme, and will not be a component of this CSR

Exploratory objectives

- To investigate the pharmacodynamic effect on biomarkers in non-tumour (mandatory) and tumour (optional)
- To obtain an assessment of efficacy of AZD6244
- To investigate whether variability in the pharmacokinetic, safety, efficacy or pharmacokinetic results could be explained by differences in the patients genotype[3]

Study design

This was a Phase I, open label, multi-centre study to assess the safety, tolerability and pharmacokinetics of a Hyd-Sulfate capsule formulation of AZD6244 in patients with advanced solid malignancies who have failed standard therapy or for which no standard therapy exists.

Target patient population and sample size

The patients (male or female, aged 18 years or older) entering this study had cancers refractory to standard therapies, or for which no standard therapies existed. Patients were of World Health Organisation performance status 0-2 (those with performance status 2 must have been stable with no deterioration over the previous 2 weeks).

Part A of the study was not formally powered, but was designed to provide adequate tolerability, safety, pharmacokinetic, and pharmacodynamic data. Part A was also designed to ensure at least 6 evaluable patients were recruited at the dose deemed to be the maximum tolerated dose (MTD). The aim of Part B (relative bioavailability, safety and tolerability) was to provide adequate data to assess whether the dose used for onward development provided at least the same AUC as the 100 mg mix and drink dose. Ten evaluable patients per sequence were considered (based on Part A data and ARRY study 0401) to be sufficient in order to enable an adequate assessment of the relative oral bioavailability of the Hyd-Sulfate capsule to the free-base suspension formulation. Twenty-eight patients were to be randomised to ensure that 20 patients completed Part B.

Thirty-one patients were enrolled into Part A (28 patients received AZD6244), and 29 patients were randomised into Part B (28 patients received AZD6244).

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

Part A: The first cohort received a 25 mg dose of AZD6244 capsule formulation (hydrogen sulfate salt, hereafter referred to as Hyd-Sulfate capsule)[4]. Subsequent cohorts were dispensed

[3] The results of the genetic study are not part of the clinical study report, and if appropriate may be pooled with genetic results from other studies and reported at a later date.

investigational product as a capsule formulation according to the dose directed by the Safety Review Committee; AZD6244 Hyd-Sulfate capsule was administered at 25, 50, 75 and 100 mg doses. Patients received a single dose of the Hyd-Sulfate capsule of AZD6244 on Day 1, followed by twice daily dosing from Day 2 onwards.

Part B: The 75 mg starting dose in Part B was derived from Part A, as directed by the Safety Review Committee. The patients received either a single dose of Hyd-Sulfate capsule formulation or free-base suspension formulation on Day 1 and 8, followed by continuous twice daily dosing of the Hyd-Sulfate capsule from Day 9 onwards. AZD6244 free-base suspension (also known as mix and drink) drug product was administered at a dose of 100 mg[5]. The suspension vehicle, a sulfobutylether β-cyclodextrin, sodium (Captisol®) aqueous solution (25% w/v), was supplied as a liquid.

Duration of treatment

In both parts patients could continue to receive AZD6244 until disease progression and as long as they were continuing to derive benefit from treatment. Patients who continued to receive treatment beyond the defined end of study were to be followed up according to the investigational site standard of care and investigator judgement. End of study was defined as the date when all patients still receiving treatment had been followed for a minimum period of 6 months.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Pharmacokinetic variables: Where appropriate, the following pharmacokinetic parameters were derived for AZD6244, N-desmethyl AZD6244 and AZD6244 amide following both a single dose and twice daily dosing: C_{max}, t_{max}, AUC, AUC_{0-12}, AUC_{0-24} CL/F, V_{ss}/F, and $t_{1/2}$.

Pharmacodynamic variables: Percentage inhibition of extracellular signal-regulated kinase (ERK) phosphorylation over time for each dose level after single doses of AZD6244. An exploratory plot of the percentage inhibition of ERK phosphorylation versus AZD6244 plasma concentration across the dose range studied was produced.

Efficacy variables: A patient's best overall response was calculated as the best response recorded from the date of first dose for each patient, using the following response categories: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Best overall response was determined programmatically based on response evaluation criteria in solid tumours (RECIST) criteria.

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[4] Batch numbers for capsule formulation: 50039A07, 50040B07, 50041J07, 52780C07

[5]Batch number for mix and drink (free-base) formulation: 42191K06; Batch number for suspension vehicle: 42191K06

Criteria for evaluation - safety (main variables)

Safety data were not formally analysed.

Safety variables: Incidence and severity of adverse events, clinical chemistry, haematology and urinalysis, vital signs, multiple-gated acquisition (MUGA) scan/echocardiogram (echo), electrocardiogram (ECG).

Statistical methods

A formal statistical analysis was not carried out on data from Part A. MTD was defined as the last dose assessed below the non-tolerated dose (a dose limiting toxicity observed in ≥2/6 patients within 22 days of commencing treatment).

Part B: In order to determine the relative oral bioavailability of the Hyd-Sulfate capsule to the free-base suspension formulation and to compare the exposures of the formulations at the MTD doses, statistical analysis from nominal days 1 and 8 was carried out on the following variables: AUC, $AUC_{(0-24)}$, C_{max} and t_{max} of AZD6244. Previous experience has shown that AUC, $AUC_{(0-24)}$ and C_{max} conform to a log-normal distribution and therefore these variables were logarithmically transformed prior to analysis.

The AZD6244 AUC and C_{max} data from Part B was analysed using an analysis of variance (ANOVA) model. The model allowed for the effect of formulation, and included factors fitted for the effect of period (ie day 1 or day 8) in which formulations were received, the effect of sequence of formulations received and subject within sequence (as a random effect). The adjusted geometric means (glsmeans) were estimated for each formulation. The formulation effect (being the ratio of Hyd-Sulfate capsule glsmean/free-base suspension formulation glsmean) was estimated, together with its 90% confidence interval. For the estimate of relative bioavailability only, AUC_{0-24} data were dose normalised prior to analysis.

The analysis of the AZD6244 t_{max} data was performed on untransformed data using a non-parametric analysis. The formulation effect, as measured by subject differences in t_{max} (Hyd-Sulfate capsule formulation – free-base suspension formulation), was analysed using a Wilcoxon signed rank test. The Hodges-Lehman estimator of median formulation effect was calculated and corresponding 90% confidence intervals constructed.

Subject population

Thirty-one patients were enrolled into Part A of the study. One patient was excluded due to incorrect enrolment, and therefore 30 patients were included in the full analysis set. Six patients were assigned to the 25 mg cohort, 8 patients at 50 mg, 7 patients at 75 mg, and 9 patients at 100 mg. Two patients did not receive study drug (1 in the 50 mg and 1 in the 100 mg cohort), and therefore 28 patients were included in the safety and pharmacokinetic analysis sets.

Thirty two patients were enrolled into Part B of the study, of whom 29 were randomised, and therefore included in the full analysis set. 14 patients were randomised to Sequence 1

(free-base suspension 1, Hyd-Sulfate capsule day 8) and 15 patients to Sequence 2 (Hyd-Sulfate capsule day 1, free-base suspension day 8). One patient randomised to Sequence 2 did not receive study drug, and therefore 28 patients were included in the pharmacokinetic and safety analysis set.

In Part A, 6 (20.0%) patients terminated the study due to an adverse event, 21 (70.0%) as their condition worsened, and 3 for other reasons (including 2 patients still ongoing on study therapy at the time of data cut-off). In Part B, 4 (13.8%) patients terminated the study due to an adverse event, 20 (69.0%) as their condition worsened, and 5 for other reasons (including 3 patients still ongoing on study therapy at the time of data cut-off).

The study population was representative of the broader clinical population of patients with advanced solid malignancies in terms of baseline and demographic characteristics.

There were no major protocol deviations that led to exclusion of patients from the safety summaries, and no exclusions were thought to have affected the quality of the data.

Summary of pharmacokinetic results

- AZD6244 PK was approximately dose proportional across the 25 to 100 mg dose range studied

- The MTD for the Hyd-Sulfate capsule formulation was 75 mg bd

- Based on dose-normalised $AUC_{0–24}$, the estimated oral bioavailability of the Hyd-Sulfate capsule (N=26) relative to the free base suspension (N=28) was 263% (90% CI = 214 to 322%), indicating a statistically significant increase in the oral bioavailability with the Hyd-Sulfate capsule compared to the free-base suspension

- The AUC_{0-24} and C_{max} glsmeans obtained at the MTD of the Hyd-Sulfate capsule (75 mg) were statistically significantly higher than those obtained at the MTD of the free base suspension (100 mg):

  – based on $AUC_{0–24}$, the exposure of the Hyd-Sulfate capsule (N=26) relative to the free base suspension (N=28) was estimated to be 197% (90% CI = 161 to 242%); based on C_{max}, 252% (90% CI = 182 to 348%, N=27 and 28 for Hyd-Sulfate capsule and free-base suspension, respectively)

  – however, there was a relatively large variation in relative bioavailability between patients, and for some the C_{max} and/or AUC_{0-24} for the 75 mg capsule was lower than that for the 100 mg suspension

- N-desmethyl AZD6244 had a similar PK profile to AZD6244, and the mean ratio of N-desmethyl AZD6244 to AZD6244 was ≤15% (maximum 29%) based on plasma C_{max} and AUC values

- Accumulation of the AZD6244 amide metabolite was observed after multiple dosing, giving a mean ratio of AZD6244 amide to AZD6244 of ≤8% (maximum 22%) based on plasma C_{max} and AUC_{0-4} values after multiple dosing with the Hyd-sulfate capsule

Summary of efficacy results

- One patient (Part A, 75 mg BD) achieved a complete response in the study after 16 weeks, this patient had *BRAF*+ve melanoma

- Nine patients in Part A and 13 patients in Part B had a best response of stable disease. Ten out of 55 (18.2%) patients (not including the patient who had a CR) had stable disease of ≥16 weeks. Seven patients in Part A and 12 patients in Part B had a best response of progressive disease, and 10 patients in Part A and 3 patients in Part B were not evaluable for response

Summary of pharmacodynamic results

- TPA-induced ERK phosphorylation in PBMCs was inhibited after administration of AZD6244, with the magnitude of inhibition being generally related to plasma concentrations of the drug

Summary of safety results

- The AE profile observed in this study was broadly consistent with that reported previously in the Investigators Brochure

- All patients in the study reported at least 1 AE. The most frequently reported AEs (regardless of dose, severity, causality or seriousness) were fatigue, dermatitis acneiforn, nausea, diarrhoea and peripheral oedema. The majority of these events were Grade 1 or 2

- Thirteen out of 28 (46.4%) patients in Part A and 20/28 (71.4%) patients in Part B reported an AE of CTCAE grade 3 or higher. The majority of events were reported by only 1 patient. Fatigue was the most commonly reported CTCAE grade 3 or higher AE, with 8 patients reporting this event

- Twelve out of 28 (42.9%) patients in Part A, and 9/28 (32.1%) patients in Part B reported an SAE in the study. The majority of SAEs were reported by only 1 patient. The most commonly reported SAE was vomiting, reported by 4 patients

- There were very few dose reductions or interruptions in the study; no patients at 75 mg bd (Part A or B) had a dose reduction

  – -7/28 (25%) patients in Part A and 11/28 (39.3%) in Part B had an AE that led to discontinuation. 14/35 (40%) of patients at 75 mg dose [Part A+B] had an AE that led to discontinuation

- There was a trend for an increase in SBP and DBP, which had resolved by week 12 of the study, and a trend for a small increase in weight (at the 75 mg bd dose for Part A+B patients the mean increase at week 8 was 1.7 kg). There was a trend for a decrease in LVEF (at the 75 mg bd dose for Part A+B patients the mean decrease at week 8 was -7.2%, range –25% to +10%)

- Mean increases in ALT, AST and ALP were observed within 1 week of initiation of AZD6244 treatment , but did not continue to rise beyond 28 days of dosing, except in patients at time points immediately prior to withdrawal due to disease progression. The majority of reported transaminase elevations occurring prior to disease progression either remained within normal limits or were a maximum increase of 1 CTCAE Grade

- Small increases in Ca:phosphate product, alkaline phosphatase, phosphate, creatinine, and urea, were observed within normal limits. Small decreases were observed in platelets, BNP, albumin, and total protein, but these remained within normal limits