Clinical Study Report Synopsis

Drug Substance Olaparib (AZD2281, KU-0059436)

Study Code D0816C00008

EudraCT Number 2013-002969-19

A Non-randomised, Open-label, Sequential, Multicentre, Two-part, Phase I Study to Assess the Effect of Rifampicin, a CYP Inducer, on the Pharmacokinetics of Olaparib Following Oral Dosing of a Tablet Formulation in Patients with Advanced Solid Tumours

Study dates: First subject enrolled: 16 December 2013
Last subject last visit: 22 May 2014

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 study was conducted at 5 sites in 2 countries.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Primary objective	Outcome variables
To investigate the effect of rifampicin on the PK of olaparib following oral dosing of the tablet formulation in patients with advanced solid tumours	– Maximum plasma concentration (C_{max}) – Area under the plasma concentration time curve from zero to the last measurable time point (AUC_{0-t}) – Area under the plasma concentration time curve from zero to infinity (AUC)
Secondary objectives	**Outcome variables**
To characterise the PK of olaparib following oral dosing of the tablet formulation in the presence and absence of rifampicin	– Time to reach maximum plasma concentration (t_{max}) – Terminal half-life ($t_{½}$) – Terminal rate constant (λ_z) – Area under the plasma concentration time curve from zero to the last measurable time point (AUC_{0-t}) – Apparent clearance (CL/F) – Apparent volume of distribution (V_z/F)
To demonstrate exposure to rifampicin	– Plasma concentrations of rifampicin during rifampicin dosing period
To demonstrate induction of CYP by rifampicin	– Plasma concentrations of 4β-hydroxycholesterol during rifampicin dosing period.
To investigate safety and tolerability of single and multiple oral doses of olaparib tablets in patients with advanced solid tumours	– Assessment of AEs, graded by CTCAE v4.0 – Physical examination – Vital signs (including BP and pulse) – Standard 12 lead ECG – Laboratory parameters (clinical chemistry, haematology, and urinalysis).

AE adverse event; BP blood pressure; CTCAE Common Toxicity Criteria for Adverse Events; CYP cytochrome P450; ECG electrocardiogram; PK pharmacokinetic.

Study design

This was a 2-part, Phase I, multicentre study in patients with advanced solid tumours. Part A was a non-randomised, open-label, 2-treatment design in which patients received 2 single

doses of olaparib, one administered concomitantly with rifampicin. Each patient received 1 single, 300 mg oral dose of olaparib (administered as 2 x 150 mg tablets) on Day 1. On Day 5, patients commenced once daily doses of rifampicin (600 mg administered as 2 x 300 mg capsules) for a period of 13 days (Days 5 to 17). On Day 14, patients received a single oral dose of olaparib 300 mg administered concomitantly with the 600 mg rifampicin dose. Patients were fasted overnight before each olaparib dose and remained fasting until 2 hours post-dose. When taking rifampicin (without olaparib), patients took their doses in the morning at least 30 minutes prior to breakfast.

In Part B, patients were allowed continued access to olaparib (300 mg twice daily [bd]) after the pharmacokinetic (PK) phase. Prior to starting Part B, patients completed a washout period of at least 7 days and not more than 14 days after the last dose of rifampicin in Part A. Part B was planned to be of 12 months' duration from the date the last patient entered this part of the study. During and after Part B, patients could continue to take olaparib, if they and the Investigator deemed it appropriate, until such time as their disease progressed, the Investigator believed they were no longer deriving clinical benefit, or they stopped taking olaparib for any other reason.

Target subject population and sample size

It was planned to recruit approximately 18 patients (male or female) with advanced solid tumours to ensure that at least 16 evaluable patients completed the study.

The study was sized to provide an estimate of the difference between olaparib PK parameters in the presence and absence of concomitant rifampicin. Based on an estimate of within-patient standard deviation from Study D0180C00024 (for log maximum plasma concentration [C_{max}]) of 0.294 for the 300 mg tablet and assuming a true interaction effect of 30% (based on simulations from in vitro data), 16 evaluable patients were required give 90% power to show that the 90% confidence interval (CI) for the rifampicin effect was entirely above 0.5 (ie, would rule out a halving of exposure in the presence of rifampicin).

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

Olaparib was supplied as 100 mg and 150 mg tablets for oral administration. Olaparib 100 mg and 150 mg tablets were manufactured by AbbVie on behalf of AstraZeneca. The 100 mg tablet was only used in Part B in the event of dose reduction. No dose reductions were allowed in Part A.

In Part A, patients received 2 single doses of olaparib 300 mg. In Part A, patients also received 13 daily doses of rifampicin 600 mg. In Part B, patients took olaparib 300 mg bd.

The batch numbers were 13-001054AZ (100 mg) and 13-001263AZ (150 mg).

Duration of treatment

In Part A, patients received 2 single oral doses of olaparib tablets 300 mg: once alone and once concomitantly with rifampicin.

In Part B, patients were planned to continue receiving olaparib at a dose of 300 mg bd for a period of 12 months after the date the last patient entered this part of the study. Patients could continue to take olaparib during and after Part B, if they and the Investigator considered it was appropriate, until such time as their disease progressed, the Investigator believed they were no longer deriving clinical benefit, or they stopped taking olaparib for any other reason.

Statistical methods

The objective of the statistical analysis in Part A was to estimate the effect of rifampicin on the PK of olaparib. Following log-transformation using natural logarithms, C_{max}, area under the plasma concentration time curve from zero to infinity (AUC), area under the plasma concentration time curve from zero to the last measurable time point (AUC_{0-t}), and 4β-hydroxycholesterol plasma concentration were analysed using a mixed-effect analysis of variance model, with treatment as a fixed effect and patient as a random effect. Point estimates and adjusted 90% CIs for the difference between treatments, for C_{max}, AUC, AUC_{0-t}, and 4β-hydroxycholesterol plasma concentration, were constructed based on the following treatment comparisons:

- olaparib + rifampicin compared to olaparib (C_{max}, AUC, and AUC_{0-t})
- Day 17 compared to Day 5 (4β-hydroxycholesterol plasma concentration)

Each confidence interval was based on the t distribution. The sum of squares of the residuals in the linear model was used to estimate the variance, which was assumed to be equal for both treatments.

The point estimate and adjusted 90% CIs were then exponentially back transformed to provide point and CI estimates for the ratio of interest. An interaction between rifampicin and olaparib was considered to have occurred if the lower limit of the 90% CI for the ratio was less than 0.5 (ie, greater than a 50% decrease in olaparib AUC or C_{max} in the presence of rifampicin, compared to olaparib alone).

An analysis of time to reach maximum plasma concentration (t_{max}) using the Wilcoxon Signed Rank Test, and the Lehmann median estimator of difference ([olaparib + rifampicin] – olaparib alone) and 90% CIs was also presented.

Rifampicin and 4β-hydroxycholesterol plasma concentrations were also presented in data listings and summaries.

Safety data were listed and summarised using descriptive statistics.

This study report contains data from Part A of the study only. Data for Part B of this study will be presented in an addendum to this report.

Subject population

In Part A, 22 patients (4 male and 18 female) were assigned to treatment and received at least 1 dose of olaparib.

During Part A of the study, 1 patient was discontinued due to death resulting from the condition under investigation and 2 patients discontinued due to worsening of the condition under investigation. The remaining 19 patients completed Part A and continued into Part B of the study. The demographic and baseline patient characteristics were representative of the intended patient population. The majority of patients (18 patients [81.8%]) had an Eastern Cooperative Oncology Group performance status ≤1, with ovary, breast, bladder and colon being the most common primary tumour locations. A total of 7 patients (31.8%) had at least 1 important protocol deviation but none resulted in exclusion of the patient from the analysis. All 22 patients who entered the study were included in both the safety and PK analysis sets.

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

When olaparib was dosed concomitantly with rifampicin on Day 14 (after 9 days of rifampicin dosing [600 mg once daily]) olaparib C_{max} was reduced (geometric mean: 2.24 µg/mL) compared with patients dosed with olaparib alone (geometric mean: 8.05 µg/mL). The point estimate of the treatment ratio for C_{max} indicates a statistically significant reduction in olaparib exposure in the presence of rifampicin by about 71% (ratio: 0.29; 90% CI: 0.24, 0.33). The AUC of olaparib was also reduced by approximately 87% in combination with rifampicin compared with olaparib alone (treatment ratio: 0.13; 90% CI: 0.11, 0.16). Similarly, AUC_{0-t} decreased by the same magnitude (treatment ratio: 0.12; 90% CI: 0.10, 0.15). The treatment ratio and 90% CI for C_{max} and AUCs were <0.5 (ie, greater than halving of the exposure). The CL/F increased by 7.6- fold and Vz/F by 9.6-fold following dosing in the presence of rifampicin. However, there was no marked change in $t_{½}$ (arithmetic mean: 15.8 hours in combination with rifampicin) compared with olaparib alone (arithmetic mean $t_{½}$: 13 hours).

Exposure to rifampicin, as determined by plasma concentrations on Days 5, 9, 14 and 17 at 2 hours after dosing with rifampicin (600 mg) were of a similar magnitude to those reported in other controlled clinical pharmacokinetic studies utilising this dosing regimen where significant drug-drug interactions have been demonstrated.

Following a once daily administration of rifampicin (600 mg) for 13 days (Days 5 to 17), mean plasma 4β-hydroxycholesterol levels increased by approximately 5-fold confirming that CYP3A4 enzyme induction had occurred in patients.

Summary of safety results

In the safety set, AEs were reported in 19 patients (86.4%). The number and type of AEs reported during this study were in line with what would be expected for this patient population and the safety profile for olaparib. The most frequently reported AEs were nausea (7 patients

[31.8%]), vomiting (6 patients [27.3%]), chromaturia (5 patients [22.7%]), and abdominal pain, decreased appetite, and headache (4 patients [18.2%] each).

During Part A, 4 patients reported 6 SAEs (nausea [n=2], decreased appetite, fatigue, convulsion and ascites). There was 1 death reported during the olaparib + rifampicin dosing period; this was not considered to be related to olaparib, was not reported as an AE and was considered to be due to progression of the condition under investigation. There were no AEs reported that led to discontinuation of olaparib treatment. Six patients (27.3%) reported AEs of CTCAE Grade 3. All other AEs in Part A of the study were ≤CTCAE Grade 2.

One clinically significant ECG abnormality was reported at screening (right bundle branch block – atrial fibrillation). There were no other clinically significant abnormalities in clinical laboratory parameters (haematological, clinical chemistry and urinalysis), vital signs or ECG data.