Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D081AC00001
Edition Number	1
EudraCT Number	2013-001255-13

A Two-part, Randomised, Open-label, Multicentre, Phase I Study to Determine the Effect of Food on the Pharmacokinetics of Olaparib Following Single 400 mg Doses of the Capsule Formulation in Patients with Advanced Solid Tumours

Study dates: First subject enrolled: 04 July 2013
Last subject last visit: 18 October 2013

Phase of development: Clinical pharmacology (I)

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

Study centres

The study was conducted at 7 sites in 3 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 food on the pharmacokinetics (PK) of olaparib following oral dosing of the capsule formulation in patients with advanced solid tumours	– Maximum plasma concentration (C_{max}) – Time to reach maximum plasma concentration (t_{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) – Apparent clearance following oral administration (CL/F) – Apparent volume of distribution (V_z/F) – Terminal rate constant (λ_z) – Terminal half-life ($t_{½}$) – Other parameters could be determined as deemed appropriate
Secondary objective	**Outcome variables**
To further investigate the safety and tolerability of olaparib following oral dosing of the capsule formulation in patients with advanced solid tumours	– Adverse events (AEs) – Physical examination – Vital signs (blood pressure and pulse) – Electrocardiogram parameters – Laboratory parameters (clinical chemistry, haematology and urinalysis)

Study design

This was a 2-part, Phase I, multicentre study in patients with advanced solid tumours. Part A was a randomised, open-label, 3-period crossover study to determine the effect of food on the PK profile of olaparib. Each patient received a single 400 mg oral dose of olaparib (given as eight 50 mg capsules) in each of the 3 treatment periods (once in the overnight fasted state, once immediately following a high-fat meal and once immediately following a standard meal), with a washout period of at least 5 and no more than 14 days between doses.

In Part B, patients were allowed continued access to olaparib (400 mg twice daily [bd]) after the PK phase. Patients could start Part B anytime after completion of PK sampling on Day 4 of Part A, or up to a maximum of 14 days after the last olaparib dose in Part A.

Target patient population and sample size

It was planned to recruit approximately 30 patients (male or female) with advanced solid tumours to ensure that at least 24 evaluable patients completed the study.

Based on the estimate of within-patient standard deviation (SD) for log AUC from Study D0810C00024 of 0.296, and assuming a true food effect difference of 30% (estimated from pre-clinical in vivo data), 24 evaluable patients were required to give 90% power of showing that the 90% confidence interval (CI) for the food effect (ratio of geometric least-squares means of AUC or C_{max} in the fed state [standard meal or high fat meal] to the fasted state) was entirely within the range of 0.59 and 1.70, ie, to exclude the possibility of a 70% increase in AUC or C_{max}.

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

Olaparib was supplied as 50 mg capsules for oral administration. Olaparib 50 mg capsules were manufactured by Patheon on behalf of AstraZeneca.

In Part A, patients received 3 single doses of olaparib 400 mg. In Part B, patients took olaparib 400 mg bd.

The batch number was 3096992R.

Duration of treatment

In Part A, patients received a single dose of olaparib 400 mg on Day 1 of each of the 3 treatments periods with a washout period of at least 5 and no more than 14 days between doses. Patients could start Part B anytime after completion of PK sampling on Day 4 of Part A, or up to a maximum of 14 days after the last olaparib dose in Part A.

In Part B, patients continued to receive olaparib at a dose of 400 mg bd for a period of 6 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 goal of the statistical analysis in Part A was to estimate the effect of food on the PK of olaparib. Following log-transformation, C_{max}, AUC and AUC_{0-t} of olaparib was analysed separately by mixed-effect analysis of variance (ANOVA), fitting terms for treatment (food condition: high fat meal, standard meal or fasted), sequence, and treatment period. Patient within sequence was treated as a random effect in the model. Point estimates and adjusted

90% CIs for the difference in treatment (standard meal or high fat meal compared to fasted) were constructed. The point estimate and adjusted 90% CIs were then back transformed to provide point and CI estimates for the ratio of interest (eg, C_{max}, AUC or AUC_{0-t} of olaparib for the high fat meal to C_{max}, AUC or AUC_{0-t} of olaparib in the fasted state). If the upper limit of the 90% CIs for the ratios of AUC, AUC_{0-t} and C_{max} were <1.70, the magnitude of the effect of food was not considered to be of clinical concern based upon exposure and tolerability data generated in the olaparib development programme.

An analysis of t_{max} using the Wilcoxon Signed Rank Test, and the Lehman median estimator of difference (standard or high fat meal compared to fasted) and 90% CIs was also presented.

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 35 patients enrolled, 32 (5 male and 27 female) were randomised and received at least 1 dose of olaparib (3 did not fulfil eligibility criteria). One patient was discontinued due to an AE, with the remainder completing Part A and continuing to Part B of the study. The demographic and baseline patient characteristics were representative of the intended patient population. The majority of patients (93.7%) had an Eastern Cooperative Oncology Group performance status ≤1, with ovary, breast and rectal being the most common primary tumour locations. The patient discontinued due to an AE was excluded from the PK analysis dataset. Data from a patient who had a history of bypass surgery were included in the PK analysis dataset, but excluded from all summaries and statistical analyses of PK data.

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

Based on the treatment ratio for AUC, olaparib exposures increased by approximately 20% when administered following a standard meal (treatment ratio: 1.21; 90% CI: 1.10, 1.33) or high fat meal (treatment ratio: 1.19; 90% CI: 1.08, 1.31). AUC_{0-t} also increased by a similar magnitude for the standard meal (treatment ratio: 1.20; 90% CI: 1.09, 1.31) and high fat meal (treatment ratio: 1.22; 90% CI: 1.11, 1.34). However, C_{max} increased by 10% following a standard meal (treatment ratio: 1.10; 90% CI: 1.02, 1.20) and there was no obvious food effect following a high fat meal (treatment ratio: 1.00; 90% CI: 0.92, 1.09), probably reflecting the delay in t_{max} of approximately 2 hours. Food had no influence on the variability of systemic exposure to olaparib with %GCV for the geometric mean AUC values in the range 65 to 86% independent of the prandial state.

Although the treatment ratios and 90% CI for the treatment ratios for AUC or C_{max} were entirely within the 0.59 to 1.70 boundary used to size the study, there were individual patients where the magnitude of increase in AUC was greater than 1.7-fold (notably 3 patients after the

standard meal where the AUC ratios were 2.00, 2.06 and 2.12, and 2 patients after the high fat meal where the ratios were 1.95 and 1.74) ie in approximately 10% of patients in each of the two "fed" arms. In approximately 20% of patients, AUC increased by >50% in the presence of food. Overall, the results of the study have shown that food (standard fed or high fat) slows the rate (delayed t_{max}) and increases the extent of absorption of olaparib by approximately 20%.

Summary of safety results

In the safety set there was a total of 67 AEs experienced by 23 (71.9%) patients. 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 AEs reported by the greatest number of patients were nausea (6 [18.8%] patients), vomiting and diarrhoea (4 [12.5%] patients each), and medical device complication and dyspepsia (3 [9.4%] patients each). All other AEs were experienced by ≤2 [6.3%] patients. There were no clinically relevant differences between the safety profiles of olaparib administered after a standard or high fat meal, compared with the fasted state, and no obvious increase in the incidence of AEs in the SOC gastrointestinal disorders on dosing days, compared with non-dosing washout days. For all treatment conditions (ie, high fat meal, standard meal and fasted state), the most frequent AEs related to olaparib were of gastrointestinal origin.

One patient discontinued due to an AE of vomiting (Common Terminology Criteria for Adverse Event [CTCAE] grade 1), and 1 patient had an SAE of urinary tract infection (CTCAE grade 3). The AE leading to discontinuation and SAE were not considered to be treatment-related. One patient experienced a treatment-related AE of fatigue (CTCAE grade 3); however, this patient had fatigue as a current medical condition at study entry, and an ECOG performance status of 2. All other AEs in Part A of the study were ≤CTCAE grade 2. There were no deaths in Part A of this study.

The number of abnormalities in clinical laboratory parameters, vital signs, electrocardiogram and physical examination data was low, with the majority considered to be consistent with the known safety profile of olaparib or the patients' underlying disease. There were no AEs in the SOC blood and lymphatic disorders.