Clinical Study Report Synopsis

Drug Substance: Olaparib (AZD2281, KU-0059436)

Study Code: D0816C00007

EudraCT Number: 2013-001892-18

A Non-randomised, Open-label, Sequential, Three-part, Phase I Study to Assess the Effect of Itraconazole (a CYP3A4 Inhibitor) on the Pharmacokinetics of Olaparib Following Oral Dosing of a Tablet Formulation, and to Provide Data on the Effect of Olaparib on QT Interval Following Oral Dosing of a Tablet Formulation to Patients with Advanced Solid Tumours

Study dates: First subject enrolled: 04 October 2013
Last subject last visit: 23 April 2015

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 11 sites in 4 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 itraconazole on the pharmacokinetics (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 infinity (AUC) – Area under the plasma concentration time curve from zero to the last measurable time point (AUC_{0-t}) if AUC is not adequately estimable
Secondary objectives	**Outcome variables**
To characterise the PK of olaparib following oral dosing of the tablet formulation in the presence and absence of itraconazole (single-dose parameters)	– 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}) if AUC is not adequately estimable – 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
To characterise the PK of olaparib following oral dosing of the tablet formulation (multiple-dose parameters)	– $t_{ss,max}$ – $C_{ss,max}$ – Minimum plasma concentration ($C_{ss,min}$) – $t_{ss,min}$ – $AUC_{0-\tau}$ – Average concentration over the dosing interval ($C_{ss,avg}$ [$_{AUC0-\tau}/\tau$]) – Fluctuation index (FI) calculated as (C_{max}-C_{min}/C_{avg}) × 100% – CL_{ss}/F – Other parameters could be determined as deemed appropriate

To demonstrate exposure to itraconazole and hydroxy-itraconazole	– Itraconazole C_{max}, $AUC_{0-\tau}$, t_{max}, and CL/F – Hydroxy-itraconazole C_{max}, $AUC_{0-\tau}$, and t_{max}
To investigate the effect of olaparib on QTc following single (Part A), and multiple (Part B) oral doses of the tablet formulation	– Electrocardiogram intervals (including QT and QTc interval)
To investigate further the safety and tolerability of olaparib tablets in patients with advanced solid tumours	– Adverse events – Physical examination – Vital signs (blood pressure and pulse) – Electrocardiogram parameters – Laboratory parameters (clinical chemistry, haematology, and urinalysis)

Study design

This was a 3-part, Phase I, multicentre study in patients with advanced solid tumours. Part A was a non-randomised, open-label, 2-treatment design. Patient received the following 2 study treatments: a single oral dose of olaparib (tablet formulation) alone and a single oral dose of olaparib administered concomitantly with itraconazole. Patients checked into the clinic on Day -2, 2 nights before the start of olaparib dosing (Day 1). Baseline digital electrocardiogram (dECG) assessments were obtained on Day -1 at clock times matched to the planned/scheduled dECG assessment times on Day 1. On Day 1, patients received a single oral dose of olaparib 100 mg in the morning after an overnight fast and remained fasting for 4 hours post-dose. Patients remained resident at the clinic until 24 hours after the first dose of olaparib.

Patients then returned to the clinic on an outpatient basis for assessments on Days 3 and 4. On Day 5, patients commenced daily doses of itraconazole (200 mg once daily [od]) for 7 days. Itraconazole doses were to be taken with a full meal, except for the dose on the morning of Day 9, which was taken after an overnight fast.

Patients returned to the clinic on the evening of Day 8. On the morning of Day 9, patients received a second oral dose of olaparib 100 mg, administered concomitantly with the itraconazole dose, after an overnight fast and remained fasting for 4 hours post-dose. Patients remained resident at the clinic until 24 hours after the second dose of olaparib. Patients then returned to the clinic on an outpatient basis for assessments on Days 11 and 12. On Days 1 and 9 of Part A patients fasted over the same time period as Day -1.

Part B of this study was an open-label study with the same patients who participated in Part A. After completion of Part A, following a wash-out period of at least 7 days and no more than 14 days between the last dose in Part A and Day -1 of Part B, and if the patient still met the study entry criteria, they were provided olaparib tablets at a dose of 300 mg twice daily (bd) for 5 days. Patients checked into the clinic on the evening of Day -2. On Day -1, baseline dECG assessments were performed at clock times matched to the dECG assessments on Day 5. Patients were discharged from the clinic on the evening of Day -1. Patients

self-administered their olaparib doses under fasted conditions (from 1 hour before to 2 hours after dosing) from Day 1 to Day 4 (morning dose) on an outpatient basis. On the evening of Day 4, patients checked back into the clinic, and received their Day 4 evening dose. Patients received their Day 5 morning dose after an overnight fast and remained fasting for 4 hours post-dose. Patients underwent dECG and PK assessments pre-dose and for 12 hours post-dose. The Day 5 dECG assessments were clock-matched to the actual times that the Day -1 dECGs were performed. Patients were discharged from the clinic after completing 12-hour assessments on Day 5, and self-administered their evening Day 5 dose of olaparib. On Day 5 of Part B patients fasted over the same time period as Day -1.

Following completion of Part B, patients could enter Part C and continue to take olaparib tablets (300 mg bd) if they and the Investigator agreed that this was appropriate. Patients were required to start Part C immediately after the last dose received in Part B and could continue to receive olaparib for a period of 12 months after the date the last patient entered this part of the study.

Target patient population and sample size

It was planned to recruit approximately 48 patients (male or female) with advanced solid tumours to ensure that at least 42 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 itraconazole. In the event that the true interaction effect was minimal (5%) and based on the estimate of within-patient standard deviation (SD) for log AUC from Studies D0180C00002 and D0180C00003 of 0.26, 42 evaluable volunteers were required to give 90% power of showing that the 90% confidence interval (CI) for the interaction effect (ratio of geometric least-squares means of AUC or C_{max} when olaparib and itraconazole were co-administered compared to administration of olaparib alone) was entirely within the range of 0.8 to 1.25.

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.

In Part A, patients received 2 single doses of olaparib 100 mg. In Part A, patients also received 7 daily doses of itraconazole 200 mg. In Part B, patients received 10 doses of olaparib 300 mg. In Part C, patients took olaparib 300 mg bd.

The batch numbers were 13-001227AZ and 13-001914AZ (100 mg); 13-001228AZ, 13-002069AZ (150 mg).

Duration of treatment

In Part A, patients received 2 single oral doses of olaparib tablets 100 mg: once alone and once concomitantly with itraconazole.

In Part B, following a washout period of at least 7 days and no more than 14 days, between the last dose in Part A and Day -1 of Part B, patients received olaparib 300 mg bd for 5 days.

In Part C, patients continued to receive 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 C, 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. Dose interruptions/permanent discontinuation of olaparib, were considered if toxicity re-occurred following re-challenge with olaparib, or if dose interruptions were considered inadequate for management of toxicity.

Statistical methods

The objective of the statistical analysis in Part A was to estimate the effect of itraconazole on the PK of olaparib. The primary PK outcome variables of olaparib area under plasma concentration-time curve from zero to infinity ([AUC] or area under plasma concentration-time curve from zero to last measurable time point [AUC_{0-t}], if AUC is not adequately estimable) and C_{max} in Part A was statistically analysed to investigate the effect of itraconazole on olaparib. Following log-transformation, C_{max}, AUC, and AUC_{0-t} of olaparib were separately analysed by mixed-effect analysis of variance (ANOVA), fitting terms for treatment as a fixed effect and patient as a random effect. Point estimates and adjusted 90% CIs for the difference between treatments (olaparib + itraconazole compared to olaparib) for C_{max}, AUC, and AUC_{0-t} were constructed. The point estimate and adjusted 90% CIs were then exponentially back transformed to provide point and CI estimates for the ratio of interest. No effect on the PK of olaparib after co-administration of itraconazole was concluded if the 2-sided 90% CIs for the ratios of AUC (and/or AUC_{0-t}) and C_{max} were within the range of 0.80 to 1.25.

An analysis of t_{max} using the Wilcoxon Signed Rank Test, and the Lehman median estimator of difference (olaparib + itraconazole compared to olaparib) and 90% CIs was also presented.

Safety data were listed and summarised using descriptive statistics.

This study report contains data from Parts A and B of the study only. Data for Part C of this study will be presented in a separate report.

Subject population

A total of 83 patients enrolled, 59 (17 male and 42 female) were randomised into Parts A and B, and received at least 1 dose of olaparib (24 did not fulfil eligibility criteria). All 59 patients completed Part A of the study. Five patients discontinued from Part B: 1 patient due to death (death was due to disease progression), 2 patients were withdrawn due to AEs, 1 patient due to clinical deterioration (vomiting grade 2 and suspicion of cerebral metastases), and 1 patient withdrew due to their own decision. One patient completed Part A, did not enter Part B, and entered Part C of the study. A total of 54 (91.5%) patients entered Part C. The demographic and baseline patient characteristics were representative of the intended patient population.

The majority of patients (96.6%) had an Eastern Cooperative Oncology Group (ECOG) performance status ≤1 at study entry, with ovary, pancreas, rectal, breast, colorectal, lung, cervix, and colon being the most common primary tumour locations.

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

There was a significant increase in C_{max} (treatment ratio 1.42; 90% CI: 1.33, 1.52) when olaparib was dosed with itraconazole compared with when olaparib was dosed alone and the rate of absorption of olaparib appeared to be slightly slower when administered in the presence of itraconazole, with a median t_{max} of 1.50 hours (range: 0.5 hours to 12 hours) compared to 1.03 hours (range: 0.5 hours to 8.25 hours) observed when olaparib was administered alone. Geometric mean AUC increased by approximately 2.70-fold (90% CI: 2.44, 2.97) when olaparib was administered in the presence of itraconazole compared with olaparib alone. Mean apparent plasma clearance (CL/F) and apparent volume of distribution were reduced when olaparib was dosed in combination with itraconazole but the mean terminal half-life of olaparib (15 hours) was unchanged.

After 5 days of repeated daily administration of itraconazole (200 mg), systemic exposures to itraconazole and its hydroxy metabolite were similar to those previously reported in clinical studies utilising the same dosing regimen that have demonstrated significant drug-drug interactions.

In the multiple daily dosing arm of the study (300 mg bd; Part B), the exposures achieved were within the range previously reported following administration of the 300 mg tablet dose under fasted conditions.

Summary of pharmacodynamic results

Pharmacodynamic (ECG) data is discussed within the safety results section.

Summary of safety results

A total of 42.4% of patients in the olaparib alone dosing period of Part A, 55.9% of patients in the olaparib + itraconazole dosing period of Part A, and 57.6% of patients in Part B experienced at least 1 adverse event (AE), the majority of which were gastrointestinal in origin, and of Common Terminology Criteria for Adverse Event (CTCAE) grade 2 or lower. 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 in the olaparib alone dosing period of Part A were diarrhoea and nausea, which were reported by 4 (6.8%) patients each, respectively. The AE reported by the greatest number of patients in the olaparib + itraconazole dosing period of Part A was constipation, which was reported by 6 (10.2%) patients. The AE reported by the greatest number of patients Part B was fatigue, which was reported by 13 (22.0%) patients. There were no clinically relevant differences between the safety profiles of olaparib administered

alone, compared with the olaparib and itraconazole administration. No new safety findings were observed for olaparib during Parts A or B of the study.

One death was reported during Part A of the study and this was related to the disease under investigation.

There was no clinically relevant effect of olaparib on the QT interval observed in this study.