Clinical Study Report Synopsis	
Drug Substance	Olaparib
Study Code	D0816C00024
Edition Number	1.0
Date	12 December 2019
EudraCT Number	2017-004269-29
NCT Number	N/A

A Phase 1, Randomised, Open-label, 4-Period Crossover Study to Develop an In Vitro-In Vivo Correlation for Olaparib Tablets in Subjects with Solid Tumors

Study Dates: First subject enrolled: 16 May 2018
Last subject last visit: 12 March 2019

Phase of Development: Clinical pharmacology (I)

International Co-ordinating Investigator: [redacted]
UZ Leuven – Campus Gasthuisberg
Herestraat 49
3000 Leuven, Belgium

Sponsor's Responsible Medical Officer: [redacted]
AstraZeneca
Gaithersburg, MD, US

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

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study Centre(s)

Three study centres in Belgium.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary		To establish a [redacted] in vitro-in vivo correlation (IVIVC) model for the tablet formulation.	In vitro-in vivo correlation (IVIVC) model parameters such as the slope, time scaling factor and time shifting factor, predictive performance parameters for the model such as the %prediction errors (%PE) for AUC and C_{max}.
Secondary	Pharmacokinetics (PK)	To evaluate the PK of the tablet formulations used in the study.	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 ($AUC_{0-\infty}$); dose normalised C_{max}, AUC, and AUC_{0-t}; apparent clearance following oral administration (CL/F), apparent volume of distribution (V_z/F), terminal rate constant (λ_z), and terminal half-life ($t_{1/2}$). Other parameters were determined if deemed appropriate.
	Safety	To evaluate the safety and tolerability of olaparib during the PK studies.	Adverse events (AEs)/serious AEs, collection of clinical chemistry/haematology, electrocardiograms, and vital sign parameters.

Study Design

This was an open-label, randomised, 4-period, 4-sequence, crossover pharmacokinetic (PK) study designed to determine in vivo relative bioavailability data from olaparib tablet variants with different size/geometry and dose, to correlate with their corresponding in vitro dissolution profiles. The duration of each dosing period was 7 days, including a washout period, with a single dose administered on Day 1 of each period. This time period between treatments ensured that the average washout period of 5 days for olaparib was covered. Subjects were randomised to a treatment sequence following a balanced Latin Squares design.

Twelve subjects with advanced solid tumours who met inclusion and exclusion criteria and provided informed consent were randomly assigned to the treatment sequences: ABCD, BDAC, CADB, or DCBA. On Day 1 of each 7-day treatment period, subjects received a single dose of either Treatment A, B, C, or D, according to the randomisation schedule. Treatments A, B, C, and D indicated single, oral dose of 25, 100, 150, and 250 mg olaparib, respectively. Subjects fasted for 8 hours prior to dosing. No food was allowed for at least 2 hours post-dose. Serial blood samples for determination of olaparib in plasma were collected for up to 72 hours after the Day 1 study treatment administration. Subjects were discharged from the study centre on Day 2 and returned to the study centre for a follow-up assessment at least 7 days after their last dose of olaparib in the PK study. No Steering Committee or Data Monitoring Committee was used in this study. After the PK sampling study, subjects could enter the post study Continued Treatment phase.

During the Continued Treatment phase, subjects could receive 300 mg olaparib tablets (2 × 150 mg tablets) twice daily, as a single agent, if, in the opinion of the Investigator, they were to benefit from treatment with olaparib tablets. No additional safety data for analysis was collected during this time.

Target Subject Population and Sample Size

The target subject population were subjects ≥ 18 years old, with solid tumours that no longer responded to or were not eligible for standard therapies and for whom there were no additional standard therapies likely to benefit them. Subjects, who in the opinion of the Investigator would have benefitted from olaparib therapy, were included if they showed normal organ and bone marrow function measured within 28 days prior to administration of study treatment. To be eligible for inclusion, subjects had to have an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 and a life expectancy of ≥ 16 weeks. Female subjects had to be postmenopausal or for women of childbearing potential, provide evidence of non-childbearing status.

A total of 12 subjects were randomly allocated to receive one of the 4 treatment sequences (ABCD, BDAC, CADB, or DCBA). All 12 subjects were evaluable.

Investigational Product and Comparator(s): Dosage, Mode of Administration, and Batch Numbers

Subjects were administered single, oral doses of olaparib (AZD2281, LYNPARZA®) 25, 100, 150, and 250 mg strength tablets in a randomised sequence.

	25 mg	100 mg	150 mg	250 mg
Manufacturing batch number	[redacted]	[redacted]	[redacted]	[redacted]
Packing batch number	[redacted]	[redacted]	[redacted]	[redacted]

Duration of Treatment

The study included a single dose of olaparib 25, 100, 150, and 250 mg tablets administered using a randomised, 4-period, and 4-sequence crossover design. The duration of each dosing period was 7 days including a washout period, with a single dose administered on Day 1 of each period.

On completion of the PK sampling study, subjects were permitted to receive olaparib tablets 300 mg (2 × 150 mg tablets) twice daily, as a single agent, in a Continued Treatment phase outside of the PK study, if they, and the Investigator agreed that this was appropriate. This Continued Treatment phase continued until the Investigator believed that the subject was no longer deriving clinical benefit, or the subject stopped taking olaparib for any other reason.

Statistical and Analysis Methods

[redacted]

[redacted]

Baseline demographics, medical history disease characteristics, as well as safety data, laboratory values and electrocardiogram (ECG) assessments were analysed. Quantitative variables were summarised using descriptive statistics, including n, mean, standard deviation, median, minimum, and maximum values by treatment sequence or treatment (dose). No imputations were made for any missing data. For qualitative variables, the population size and the percentage (of available data) for each class of the variable were presented. Percentages were rounded to one decimal place.

Subject Population

This was a multicentre study conducted at 3 study centres in Belgium. Twenty-three subjects were enrolled, of which 18 subjects were randomised and received treatment.
Fourteen (77.8%) subjects received all planned doses of olaparib, while 4 (22.2%) subjects discontinued treatment and subsequently discontinued from the study.

Of the 18 subjects randomised, all (18 subjects) were included in the Safety analysis set.
Twelve subjects were included in the IVIVC modelling analysis set; 3 other subjects were excluded due to not having the full PK sampling over the 4 treatment periods, 2 other subjects due to important protocol deviations and 1 other subject due to not being evaluable ([redacted] was excluded from the IVIVC analysis set).

Overall, the median age of subjects was 63.0 years (range: 29 to 84 years), the majority were female (13 [72.2%]), and all were White. Overall, the median body mass index was 23.30 kg/m^2 (range: 16.7 to 37.0 kg/m^2).

The ECOG status at Screening for most subjects was 1 (11 [61.1%] subjects; 7 [38.9%] subjects had an ECOG status of 0) and for subjects with known American Joint Committee on Cancer staging, 8 (50.0%) subjects had Stage IV disease at primary diagnosis. The most common primary tumour locations were the ovary (6 [33.3%] subjects), breast (5 [27.8%] subjects) and pancreas (4 [22.2%] subjects). All (18 [100.0%]) subjects had metastatic disease.

All subject demographics and disease history were in line with the protocol inclusion and exclusion and inclusion criteria, in this study population of subjects with malignant solid tumours.

Summary of Efficacy Results

Not applicable.

Summary of Pharmacokinetic Results

[redacted]

Summary of Safety Results

No AEs with outcome of death were reported. Overall, 1 (5.6%) subject reported 2 SAEs, recorded as such due to prolonged hospitalisation (pyelonephritis and female genital tract fistula, both Grade 3 in severity and both not considered related to olaparib by the Investigator).

No AEs/SAEs leading to discontinuation of the study treatment or the study, or AEs of special interest were reported.

Overall, 10 (55.6%) subjects reported a total of 30 AEs. Of these, 4 (22.2%) subjects reported 4 AEs related to olaparib. There was little difference in the numbers of subjects and AEs reported among the different olaparib doses; 6 (37.5%) subjects reported 14 AEs on 25 mg, 7 (43.8%) subjects reported 12 AEs on 100 mg, 5 (31.3%) subjects reported 10 AEs on 150 mg and 6 (35.3%) subjects reported 19 AEs on 250 mg.

Most subjects had low grade events; 6 (33.3%) subjects experienced Common Terminology Criteria for Adverse Events Grade 1 AEs and 3 (16.7%) subjects experienced Grade 2 AEs. Adverse events of Grade 3 were reported for 1 (5.6%) subject; PTs: pyelonephritis and female genital tract fistula. No AEs of Grade 4 or Grade 5 were reported.

The most common AEs by Preferred Term (PT) were: decreased appetite, abdominal pain, diarrhoea, nausea, and fatigue (2 [11.1%] subjects each).

Overall, 4 (22.2%) subjects reported AEs considered related to olaparib by the Investigator: gastro-oesophageal reflux disease (1 [5.6%] subject, Grade 1 event), headache (1 [5.6%] subject, Grade 1 event) and nausea (2 [11.1%] subjects, both Grade 1 events).

From the Investigator's Brochure, it is noted that toxicities considered to be associated with administration of olaparib include haematological effects (anaemia, neutropenia, lymphopenia, leukopenia, thrombocytopenia, mean corpuscular volume elevation), decreased appetite, nausea and vomiting, diarrhoea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache, dizziness, hypersensitivity, rash, dermatitis, cough, and dyspnoea.

Overall, clinical laboratory and other safety assessments were in line with the reported safety profile of olaparib and the subject population in the study, ie, adult subjects with advanced solid tumours.

Conclusion(s)

- [redacted]
- Olaparib 25, 100, 150, and 250 mg was generally safe and well-tolerated by the population of adult subjects with advanced solid tumours in this study.