Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00010 (KU36-37)
Edition Number	1
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Open, Non-randomised, Single Centre Phase I Study to Assess the Metabolism, Excretion and Pharmacokinetics of a Single Oral 100 mg Dose of [^{14}C]-olaparib in Patients with Advanced Solid Tumours Refractory to Standard Treatments

Study dates: First patient enrolled: 04 April 2008
Last patient last visit: 17 September 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)

This was a single-centre study conducted by:

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Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
The primary objective of the study was to characterise the metabolism, excretion and pharmacokinetics of a single oral dose of 100 mg [^{14}C]-radiolabelled olaparib in patients with solid metastatic tumours.	The plasma concentration of total radioactivity; the whole blood concentration of total radioactivity; the ratio of whole blood to plasma total radioactivity concentrations at individual time points; the plasma concentrations of olaparib; the ratio of plasma olaparib to plasma total radioactivity concentrations at individual time points; the percentage of the radioactive dose excreted in the urine and faeces; the cumulative percentage of the radioactive dose recovered in the urine and faeces by the end of each collection period; the percentage of total radioactive dose excreted/recovered overall; derived pharmacokinetic parameters for olaparib, AUC, $AUC_{(0-t)}$, $t_{1/2\lambda z}$, MRT, CL_R (if present, olaparib only), CL/F and V/F (olaparib only); plasma olaparib and total radioactivity: C_{max}, t_{max}, metabolite profiles in plasma and excreta; and identification of major metabolites.[a]
Secondary	**Secondary**
To evaluate the safety and tolerability of olaparib by assessment of adverse events, laboratory findings and vital signs.	Physical examination, ECOG performance status, clinical chemistry, haematology, urinalysis, blood pressure, heart rate, ECG, AEs throughout the study.
To provide plasma and excreta samples for future studies to investigate metabolite profiles and characterise human metabolites.[a]	
To make a preliminary evaluation of clinical response as measured by objective tumour response rates.	Response Evaluation Criteria In Solid Tumours (RECIST) guidelines.

[a] The results from metabolite analyses are being reported separately.

Study design

This was an open, non-randomised, single centre mass balance study to investigate the metabolism, excretion and pharmacokinetics of [^{14}C]-olaparib in patients with advanced solid tumours refractory to standard treatments. Each patient was to receive a single oral 100 mg dose of [^{14}C]-olaparib (120 μCi; 4.44 MBq), composed of one 50 mg [^{14}C]-olaparib capsule and one 50 mg non-radiolabelled olaparib capsule. Once excreta levels fell below the level of detection for radioactivity, patients who were free from intolerable toxicity and, in the investigator's opinion, were eligible to continue treatment received twice-daily (bd) dosing with 100 mg (2 x 50 mg capsules) non-radiolabelled oral olaparib capsules.

Target patient population and sample size

Patients were ≥18 years of age, had histologically confirmed advanced tumour refractory to standard therapies, had an ECOG performance status of 0 to 2, and had adequate bone marrow, hepatic, and renal function. Six patients were to be recruited into this study as this number of patients was deemed optimal to gain adequate information whilst exposing as few patients as possible to the study medication and procedures. A population of 3 males and 3 females was preferred with recruitment conducted so that at least 2 male patients and 2 female patients would participate in the study. However, due to misinterpretation of the protocol by the investigational site only female patients were enrolled and a total of 6 female patients were treated in this study.

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

Table S2 Details of investigational product

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
[^{14}C]-olaparib	50 mg Vcaps® Hydroxypropyl Methylcellulose Capsugel® Capsules, which are not banded or enteric coated. Oral administration once at Visit 2.	AstraZeneca	F13551	P7433
olaparib	50 mg Vcaps® Hydroxypropyl Methylcellulose Capsugel® Capsules, which are not banded or enteric coated. Daily oral administration.	Quay Pharmaceuticals Ltd.	BMR/07/ 535/A	PLR/07/535/ A/H

Duration of treatment

At Visit 2 patients received a 100 mg single oral dose of [^{14}C]-olaparib formulation (composed of one 50 mg [^{14}C]-olaparib capsule and one 50 mg non-radiolabelled olaparib capsule), containing nominally 120 μCi; 4.44 MBq.

Dosing with non-radiolabelled olaparib could begin at Visit 3 provided that [^{14}C] radioactivity was ≤3 x background in the urine and faeces. Patients were permitted to commence twice-daily (bd) oral dosing with 100 mg non-radiolabelled olaparib (2 x 50 mg capsules). Patients could then continue to receive treatment assuming that they remained free from intolerable toxicity and, in the investigator's opinion, were receiving some benefit from treatment with olaparib.

Statistical methods

All data are listed and summarised using appropriate descriptive summary measures. All statistical analyses were performed using SAS statistical software (Version 8.01). No formal statistical presentation of the data was planned.

Patient population

Seven female patients were enrolled in the study, of which 1 was withdrawn without treatment. The remaining 6 patients all received treatment with [^{14}C]-olaparib (mass balance evaluable population) and then continued to receive treatment after Visit 2 (continued supply population). The 6 patients ranged in age from 34 to 72 years. The primary sites of disease were ovary (4 patients) and breast (2 patients), with duration of disease that ranged from approximately 1 to 11 years. Of the 7 patients enrolled in the study, 4 were removed from the study in order to continue treatment on compassionate use of the study drug at an increased dose. These 4 patients were all assessed with stable disease and had been on-study for 77 to 162 days. Based on new preliminary unvalidated data from another study involving patients with BRCA-/- mutations treated with either olaparib 100 mg bd or 400 mg bd, the investigator requested that, if it was determined to be in an individual patient's best interest and, if following discussion with the patient about this new information and she was in agreement, then she should be allowed the option to receive the higher dose of 400 mg bd. The remaining 3 patients were removed due to disease progression; 2 were treated and 1 was removed from the study without being treated due to rapidly progressing disease symptoms.

Summary of pharmacokinetic results

It should be noted that Patient 001-01-0003 was mis-dosed, receiving the full dose of radioactivity (120 μCi; 4.44 MBq) but only half the dose of olaparib (50 mg). As a result, mean data generated from olaparib measurements (eg, pharmacokinetic data) is presented excluding this patient whilst excretion data, calculated using radioactivity data, includes this patient.

After administration of a 100 mg oral dose of olaparib, absorption was rapid, with maximum plasma concentrations (gmean 3556 ng/mL) observed at 1.5 to 2 hours after dosing. The concentrations declined polyphasically, falling below the limit of quantification of the assay by 16 to 24 hours after dosing. The gmean AUC was 19856 ng.h/mL. The terminal half-life of olaparib was between 2.4 and 4.7 hours in all patients who received the full 100 mg dose of compound except Patient 001-01-3007 who displayed a different distribution and elimination profile and had an estimated terminal half-life of 149 hours. Oral clearance was moderate, typically between 4 and 14 L/h (excluding Patient 001-01-3007). The oral volume of

distribution was not extensive, generally being between 20 and 50 L (excluding Patient 001-01-3007).

Approximately 15% of the dose was excreted as unchanged olaparib in the urine. Renal clearance was slightly higher than the rate of renal filtration implying there may be a small contribution of active secretion into the urine.

Two patients exhibited poor faecal elimination with small or no faecal samples produced for a significant amount of time (up to 96 hours for Patient 001-01-3002 and up to 72 hours for Patient 001-01-3007). Excluding data from these 2 patients with poor faecal recovery, the mean total recovery was 97.2% of the administered radioactive dose recovered over 168 hours; comprising of 55.5% in the faeces and 41.7% in the urine. Including all the patient data (over 144 or 168 hours), a mean total of 85.8% was achieved, with 41.8% in the faeces and 44.1% in the urine.

Summary of pharmacodynamic results

Table S3 Summary of overall best response (intent-to-treat population)

Overall best response (RECIST)	Overall
Number of patients[a]	7
Stable disease (SD)	4 (57.1%)
Progressive disease (PD)	2 (28.6%)
Not evaluable/not applicable	1 (14.3%)

[a] Number of patients used as denominator to calculate percentages.

Summary of safety results

Table S4 Summary of patients with treatment-emergent adverse events (safety evaluable population)

Treatment-emergent adverse events[a]	Mass Balance (N=6)	Continued Supply (N=6)	All Phases[b] (N=6)
Number of patients with:			
Any TEAEs	4	6	6
Drug-related[c] TEAEs	2	5	5
TEAEs of CTCAE grade 3, 4 or 5	0	1	1
Drug-related[c] TEAEs of CTCAE grade 3, 4 or 5	0	1	1
TEAEs with outcome of death	0	0	0
SAE (including events with outcome of death)	0	0	0
SAE with outcome other than death[d]	0	0	0
TEAEs leading to discontinuation of treatment	0	0	0
Drug-related[c] TEAEs with outcome of death	0	0	0

[a] Patients with **multiple events** in a category are counted **once** in that category. Patients with events in more than one category are counted in each category. Includes TEAEs and AEs occurring post-treatment during the 30 day f/u. TEAEs are defined as all AEs that occurred after the first dose of study medication or within 30 day post-treatment period.

[b] Patients are only counted **once** if the same event is in the mass balance and the continued supply phases.

[c] Relationship to olaparib = Yes.

[d] All patients experiencing an SAE with non-fatal outcome (regardless if they later had a fatal SAE).

In this study a single dose of [^{14}C]-olaparib followed by continued treatment with non-radiolabelled supply was well tolerated by 6 female patients with solid tumours. Five patients had study drug-related TEAEs during the study. The only study drug-related TEAE reported during the mass balance phase was fatigue (2 events). During the continued supply phase, the only TEAEs considered related to study therapy were fatigue (n=3), nausea (n=3), dyspepsia (n=1) and headache (n=1). All were CTCAE grade 1 or 2 in severity with the exception of 1 patient who reported study drug-related CTCAE grade 3 fatigue; CTCAE grade 3 anaemia considered unrelated to study therapy was reported for the same patient. There were no clinically important changes in any clinical laboratory safety parameters.