AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2281
Study Code	D0810C00024
Edition Number	2
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EudraCT Number	2008-003697-18

A phase I, randomised, 2 period cross over study to determine the comparative bioavailability of two different oral formulations of AZD2281 in cancer patients with advanced solid tumours

Study dates:	First subject enrolled: 27 October 2008 Data cut-off: all patients in the PK, CSP, CSEP and dose escalation cohort of the CSEP (Groups 3-5.2, 6): 24 January 2012 Data cut-off: all patients in Group 8: 21 August 2013 Last subject last visit: Ongoing at the time of CSR finalisation
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)

Ten (10) sites in 4 countries (United Kingdom, Switzerland, Belgium and Australia) enrolled and randomised patients into the study.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority[a]	**Type**	**Description**	**Description**
Primary	Pharmacokinetic	Pharmacokinetic Phase Primary Objective: To determine the comparative bioavailability of the new Melt-extrusion (tablet) formulation of olaparib compared to the existing Gelucire® 44/14 (capsule) formulation.	PK assessment: The analysis of C_{max}, AUC_{0-t}, AUC and the respective tablet:capsule ratios of C_{max}, AUC_{0-t}, AUC.
Primary	Safety	Continued Supply Phase Primary Objective: To enable patients to continue taking olaparib. Safety and tolerability data will be collected to further determine the safety and tolerability of the Gelucire® 44/14 (capsule) formulation of olaparib in these patients.	Safety and tolerability: AEs, physical examination, vital signs including BP, pulse and body temperature ECG and laboratory findings including clinical chemistry, haematology and urinalysis.
Primary	Safety	Continued Supply Expansion Phase Primary Objective: To compare the safety and tolerability profile of the Melt-extrusion (tablet) and Gelucire® 44/14 (capsule) formulation of olaparib in all patients.	Safety and tolerability: AEs, physical examination, vital signs including BP, pulse and body temperature ECG and laboratory findings including clinical chemistry, haematology and urinalysis.

Objective			Outcome Variable
Priority[a]	**Type**	**Description**	**Description**
Primary	Safety	Dose Escalation Phase of the continued supply expansion Primary Objective: To determine the safety and tolerability profile of higher doses than 200 mg bd, of the Melt-extrusion (tablet) formulation (Groups 3 onwards) and to compare the safety and tolerability profile of higher doses than 200 mg bd, of the Melt-extrusion (tablet) formulation with 400 mg bd Gelucire® 44/14 (capsule) formulation of olaparib (Groups 6 and 7). To determine the safety and tolerability profile of selected tablet dose schedules of the Melt-extrusion (tablet) formulation (Group 8).	Safety and tolerability: AEs, physical examination, vital signs including BP, pulse and body temperature ECG and laboratory findings including clinical chemistry, haematology and urinalysis.
Secondary	Pharmacokinetic	PK Phase Secondary Objective: To generate single dose PK data for the Melt-extrusion (tablet) formulation in man, and to generate information on dose linearity for the Melt-extrusion (tablet) formulation.	PK assessment: The analysis of C_{max}, t_{max}, AUC_{0-t}, AUC, AUC_{0-12}, t_{last}, λz, $t_{1/2}$, CL/F and Vz/F. Dose normalised C_{max}, AUC_{0-t} and AUC.
Secondary	Pharmacodynamic	PK Phase Secondary Objective: To compare the extent of PARP inhibition achieved in peripheral blood mononuclear cells (PBMCs) following dosing of both the Melt-extrusion (tablet) formulation and existing Gelucire® 44/14 (capsule) formulation.	PARP inhibition in PBMCs.
Secondary	Safety	PK Phase Secondary Objective: To determine the safety and tolerability of olaparib for both the Melt-extrusion (tablet) formulation and Gelucire® 44/14 (capsule) formulations.	Safety and tolerability: AEs, physical examination, vital signs including BP, pulse and body temperature, ECG and laboratory findings including clinical chemistry, haematology and urinalysis.
Secondary	Pharmacokinetic	Continued Supply Expansion Phase Secondary Objective: To compare (within individual patients in Group 2 and between patients in Group 1) the steady state exposure achieved with 200 mg bd Melt-extrusion (tablet) formulation and 400 mg bd Gelucire (capsule) formulation.	Steady state PK: PK parameters for Group 1: $C_{max,ss,}$ $C_{min,ss}$ and AUC_{ss}. For Group 2: $t_{max,ss}$ and individual ratios of AUC_{ss} (tablet:capsule), $C_{max,ss}$ (tablet:capsule) and $C_{min,ss}$ (tablet:capsule).

Objective			Outcome Variable
Priority[a]	**Type**	**Description**	**Description**
Secondary	Efficacy	Continued Supply Expansion Phase Secondary Objective: To describe the efficacy data observed in patients treated with the capsule and the Melt-extrusion (tablet) formulation.	Tumour size: Tumour size was defined at the sum of the longest diameters for all target lesions. For each patient, the percentage change from baseline was calculated for each schedule and unscheduled visit. Progression-free survival (PFS): PFS was defined as the time from randomisation to the earlier date of radiological progression (per RECIST criteria) or death by any cause in the absence of objective progression. Objective response rate (incorporating best overall response): Best overall response was calculated based on the overall visit responses from each RECIST assessment. It was the best response a patient had had during their time in the study up until RECIST progression or the last evaluable assessment in the absence of RECIST progression. PFS by RECIST or CA-125: Progression or recurrence based on serum CA-125 levels was defined on the basis of a progressive serial elevation of serum CA-125 (GCIG criteria). Objective response rate by RECIST or CA-125: CA-125 response was determined from the GCIG criteria. Percentage change in CA-125: For each patient, the percentage change from baseline in CA-125 level was calculated for each scheduled and unscheduled visit.

Objective			Outcome Variable
Priority[a]	**Type**	**Description**	**Description**
Secondary	Pharmacokinetic	Dose Escalation Phase of the continued supply expansion Secondary Objective: To determine the single dose and steady state exposures achieved with higher doses of olaparib Melt-extrusion (tablet) formulation.	Single dose and steady state exposures: PK parameters were derived for the tablet and capsule formulation as follows: - Groups 3-7: Single dose parameters (Day 1 C_{max} and AUC_{0-12}); - Groups 3, 4, 5, 5.1, 5.2: Multiple dose parameters (Day 29 $C_{max,ss}$, $C_{min,ss}$, AUC_{ss}); - Group 6: Multiple dose parameters (Day 29 and Day 57 $C_{max,ss}$, $C_{min,ss}$, AUC_{ss}); - Group 8: Single dose parameters (Day 1 C_{max} and $AUC_{0-8,}$ AUC_{0-12} or AUC_{0-24} as appropriate to the dosing regimen), multiple dose parameters (Day 8 and Day 57 $C_{max,ss}$, $C_{min,ss}$, AUC_{ss}) and dose normalised C_{max}, AUC_{0-12}, $C_{max,ss}$, $C_{min,ss}$ and $AUC_{ss.}$
Secondary	Pharmacokinetic	Dose Escalation Phase of the continued supply expansion Secondary Objective: To compare between patients the single dose and steady state exposures of olaparib achieved with selected tablet doses and the 400 mg bd capsule dose	Single dose and steady state exposures: PK parameters were derived for the tablet formulation and the capsule formulation: - Group 6: Single dose parameters (Day 1 C_{max} and AUC_{0-12} and multiple dose parameters (Day 29 and Day 57 $C_{max,ss}$, $C_{min,ss}$, AUC_{ss}); - Group 8: Single dose parameters (Day 1 C_{max} and $AUC_{0-8,}$ AUC_{0-12} or AUC_{0-24} as appropriate to the dosing regimen) and multiple dose parameters (Day 8 and Day 57 $C_{max,ss}$, $C_{min,ss}$, AUC_{ss}).

Objective			Outcome Variable
Priority[a]	**Type**	**Description**	**Description**
Secondary	Efficacy	Dose Escalation Phase of the continued supply expansion Secondary Objective: To describe the efficacy data observed in patients treated with the Gelucire® 44/14 (capsule) formulation and the Melt-extrusion (tablet) formulation.	PFS: PFS was defined as the time from randomisation to the earlier date of radiological progression (per RECIST criteria) or death by any cause in the absence of objective progression. Objective response rate (incorporating best overall response): Best overall response was calculated based on the overall visit responses from each RECIST assessment. It was the best response a patient had had during their time in the study up until RECIST progression or the last evaluable assessment in the absence of RECIST progression. Tumour size: Tumour size was defined as the sum of the longest diameters for all target lesions. For each patient, the percentage change from baseline was calculated for each schedule and unscheduled visit. PFS by RECIST or CA-125: Progression or recurrence based on serum CA-125 levels was defined on the basis of a progressive serial elevation of serum CA-125 (modified GCIG criteria). Objective response rate by RECIST or CA-125: CA-125 response was determined from the GCIG criteria. Percentage change in CA-125: For each patient, the percentage change from baseline in CA-125 level was calculated for each scheduled and unscheduled visit.
Secondary	Pharmacokinetic	Dose Escalation Phase of the continued supply expansion Secondary Objective (Group 8): To obtain a preliminary assessment of the effect of food on the exposure to olaparib following dosing of the Melt-extrusion (tablet) formulation.	PK assessment: A preliminary assessment of the effect of food was made by comparison of the Day 8 (fed) $C_{max,ss}$ and AUC_{ss} PK parameters with the Day 1 (fasted) C_{max} and AUC_{0-24} data from patients in the 400 mg od tablet treatment arm of Group 8.

Objective			Outcome Variable
Priority[a]	**Type**	**Description**	**Description**
Exploratory	Biomarker	Groups 6, 7 and 8: To perform exploratory biomarker analysis and to correlate biomarker data with disease progression/response to therapy from optional historical tumour samples collected from gBRCA patients.	Biomarker analysis: Exploratory biomarker analysis of the activity of olaparib and correlation with disease progression/response to therapy were conducted. If available, archival tumour samples from patients enrolled into Group 6 were collected in order to achieve this objective (this was also planned for Group 7).
Exploratory	Safety	Group 8: To further characterise the nature and profile of common low grade AEs associated with olaparib (nausea, vomiting and fatigue) to maximise understanding of these AEs and inform future data collection and CRF design.	Safety and tolerability: Nausea, vomiting and fatigue questionnaires.

[a] There are 2 exploratory objectives in this study that are not reported within this CSR.
PARP inhibition in PBMC's have been analysed and reported by AstraZeneca.
Efficacy: PFS by RECIST or CA-125, and percentage change in CA-125, and objective response rate by RECIST or CA-125: These results are discussed in the CSR only.

AE: Adverse event; BP: Blood pressure; CA-125: Cancer antigen 125; CRF: Case report form; CSP Clinical study protocol; ECG: Electrocardiogram; gBRCA: Confirmed genetic breast cancer type gene mutation; GCIG: Gynecologic Cancer Intergroup; PARP: Poly-(ADP-ribose) polymerase; PBMC: Peripheral blood mononuclear cells; PK: Pharmacokinetic; RECIST: response Evaluation Criteria in Solid Tumours; SAP: Statistical analysis plan.

Study design

The first part of the study consisted of a PK Phase (PKP) to establish the comparative bioavailability of the tablet formulation compared to the capsule formulation and to assess the safety and tolerability of both formulations. Patients took part in two randomised treatment periods each separated by a washout period of 6 to 14 days. Patients were randomised (assigned 1:1) into either Sequence 1 (a single capsule dose followed by a single tablet dose) or Sequence 2 (a single tablet dose followed by a single capsule dose). Patients in Cohort 1 received a single 50 mg capsule dose and a single 25 mg tablet dose. Patients in Cohort 2 received a single 100 mg capsule dose and a single 50 mg tablet dose. Cohorts 1 and 2 recruited consecutively, with Cohort 1 recruiting first, immediately followed by Cohort 2. Following the completion of Cohorts 1 and 2, PK analysis of the data defined the higher dose level for the tablet dose in Cohort 3.

The Continued Supply Phase (CSP) was scheduled seven (7) days after the end of treatment in the PK Phase. Following completion of the PK Phase, patients were allowed to continue to receive treatment with the capsule dose (400 mg orally bd) on a continuous basis as long as they remained free from intolerable toxicity and, in the Investigator's opinion, were receiving

some clinical benefit from treatment with olaparib and did not meet any other discontinuation criteria.

The second part of the study consisted of the Continued Supply Expansion Phase (CSEP) which consisted of Group 1 and Group 2:

- Patients would be recruited to Group 1 to assess the multiple dose safety profile of the tablet formulation in a comparative setting and obtain an assessment of comparative tumour activity of the tablet and capsule doses. Group 1 patients were randomised (based on primary tumour type of breast cancer or ovarian cancer) in a 1:1 ratio to be treated with either the 200 mg bd tablet or 400 mg bd capsule dose. Patients in Group 1 would be allowed to continue on AZD2281 for as long as they were free of intolerable toxicity and, in the opinion of the investigator, were deriving some clinical benefit.

- Patients would be recruited to Group 2 which would directly compare the steady state PK of the capsule and the chosen dose of the tablet formulation. The Group 2 patients were randomly assigned a treatment sequence as follows: Treatment Sequence 1 (200 mg bd tablet until Day 8 followed by 400 mg bd capsule until Day 15) or Treatment Sequence 2 (400 mg bd capsule until Day 8 followed by 200 mg bd tablet until Day 15). After Day 15, it was planned that all patients would receive the 200 mg bd tablet until treatment discontinuation.

In order to investigate higher doses of the tablet, the third part of the study was opened. This was the Dose Escalation Phase of the CSEP, the aim of which was to assess the safety, tolerability and pharmacokinetics of higher tablet doses than 200 mg bd. Patients would be recruited to each of the following dose levels, starting at Group 3 and only escalating to the next group if the dose was tolerated: Group 3 (250 mg bd tablet dose), Group 4 (300 mg bd tablet dose), Group 5 (350 mg bd tablet dose) and Group 5.1 (400 mg bd tablet dose). If the 400 mg bd tablet dose was tolerated, dose escalations would continue to Groups 5.2, 5.3 etc. Dose increases would be at the discretion of the Safety Review Committee (SRC) and would continue until the SRC agreed that no further doses should be explored. Once entered into the study, patients commenced dosing on Day 1 and PK sampling was performed to obtain PK information after the first dose and at steady state. The SRC reviewed all of the available data after the first 3 patients who had received one cycle of treatment (28 days). If no dose-limiting toxicity (DLT) occurred in a group, a decision was made to proceed to next dose group. If 1 patient experienced a DLT, the study continued until all 6 patients had received 28 days of study treatment before deciding whether to escalate to the next dose level. If $\geq$2 patients out of the group of 6 experienced a DLT within the first 28 days of treatment, the applicable dose was considered not tolerable.

Following the completion of the dose escalation tolerability assessment up to the 400 mg bd tablet dose, it was planned to randomise patients with confirmed genetic BRCA 1/2 ovarian or breast cancer to Group 6 to assess the multiple dose safety profile of the tablet in a comparative setting (a randomised comparison between the tablet and capsule formulation).

The patients were randomised in a 1:1:1 ratio to the following active treatment arms: Treatment A (a tablet dose between 250 mg and the higher dose taken into the expansion phase that has been shown to be safe and tolerable), Treatment B (400 mg bd capsule dose) or Treatment C (400 mg bd tablet dose [or lower if the 400 mg bd dose was not tolerated]). If the 300 mg bd tablet dose was not tolerated, then patients in Group 6 would be randomised to the 400 mg bd capsule dose or the 250 mg bd tablet dose. Treatment C would not be included in Group 6 and it was then planned that approximately 30 patients would be randomised in a 1:1 ratio to either Treatment A or B.

Dose escalation would continue in parallel with Group 6 beyond 400 mg bd tablet until the SRC agreed that not further doses were to be explored. If dose escalation continued beyond 400 mg bd tablet, following the completion of the dose escalation tolerability assessment up to a dose defined by the SRC, it was planned to randomise patients to Group 7 to assess the multiple dose safety profile of the tablet in a comparative setting. The patients would be randomised on a 1:1 ratio to the following active treatment arms: Treatment A (the highest bd tablet dose that would have been deemed tolerable by the SRC following the dose escalation phase) or Treatment B (400 mg bd capsule). Randomisation would have been stratified based on primary tumour type (breast cancer or ovarian cancer). There would have been at least 10 gBRCA ovarian patients in each arm.

Following the completion of Group 6, it was planned to randomise confirmed gBRCA1/2 ovarian cancer patients to Group 8 to assess the multiple dose safety profile of the tablet in differing dose schedules (randomised comparison between the different tablet dose schedules). The patients were randomised on a 1:1:1:1 ratio to the following dosing schedules: Schedule A (200 mg tds tablet continuous dosing), Schedule B (250 mg tds tablet [intermittent] 2 weeks on study drug, 1 week off study drug), Schedule C (400 mg bd tablet [intermittent] 1 week on study drug, 1 week off study drug) or Schedule D (400 mg od tablet continuous dosing).

Target subject population and sample size

The target population included male and female patients >18 years of age with an advanced solid tumour, which was refractory to standard therapies or for which no suitable effective standard therapy existed. For the patients who would be recruited into Groups 1, 6, or 7 or 8 and would receive continuous treatment with the tablet or capsule formulation (Group 8 patients would receive tablet formulation only), the target population would be further defined as patients with confirmed genetic BRCA1/2 ovarian or breast cancer (Group 8: confirmed genetic BRCA1/2 ovarian only [including primary peritoneal and fallopian tube cancers]).

In the PK Phase of this study, it was planned to randomise 6 patients per cohort. In the CSEP, approximately 20 gBRCA patients would be recruited to Group 1 and it was planned to recruit 6 patients to Group 2. In the dose escalation phase of the CSEP (Groups 3, 4, 5, 5.1, 5.2, etc.), it was planned to recruit up to approximately 48 patients in sequential groups (a minimum of 6 patients each time). In Group 6, it was planned to randomise approximately 45 patients. If dose escalation continued beyond 400 mg bd tablet, it was planned to randomise approximately 30 patients to Group 7. In Group 8, it was planned to randomise approximately 60 patients.

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

The details of the investigational products are given in Table S2. The investigational product, olaparib, was supplied in two presentations. The first presentation was a banded white HPMC size 0 capsule, with a nominal fill weight of 500 mg. The capsules contained a 10% w/w suspension of the drug substance (olaparib) in a waxy solid (Gelucire 44/14®). The second presentation was green, film-coated tablets containing either 25 mg, 100 mg or 200 mg olaparib which were used in the PK phase and CSEP.

Table S2 Details of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer	Batch number
Olaparib (Gelucire® 44/14 [capsule] formulation)	50 mg capsule Oral use only	Patheon Inc	See CSR Appendix 12.1.6.
Olaparib (Melt-extrusion [tablet] formulation)	25, 100 and 200 mg tablets Oral use only	Soliqs	See CSR Appendix 12.1.6.

Duration of treatment

PK Phase: Cohort 1 (single dose 50 mg capsule and single dose 25 mg tablet crossover; washout of 6-14 days between doses), Cohort 2 (single dose 100 mg capsule and single dose 50 mg tablet crossover; washout of 6-14 days between doses) or Cohort 3 (single dose capsule and single dose tablet crossover [defined following completion of Cohorts 1 and 2]; washout of 6-14 days between doses). Seven (7) days after the end of treatment, patients would commence with the CSP (capsule dose) on a continuous basis until treatment discontinuation.

CSEP: Group 1: Tablet dose (200 mg bd) or capsule dose (400 mg bd) until treatment discontinuation.

CSEP: Group 2: Tablet dose (200 mg bd) for 1 week and capsule dose (400 mg bd) for 1 week (randomised crossover design). After Day 15, patients would receive the 200 mg bd tablet until treatment discontinuation.

CSEP: Group 3: 250 mg bd tablet dose until treatment discontinuation.

CSEP: Group 4: 300 mg bd tablet dose until treatment discontinuation.

CSEP: Group 5: 350 mg bd tablet dose until treatment discontinuation.

CSEP: Group 5.1: 400 mg bd tablet dose until treatment discontinuation.

CSEP: Group 5.2, 5.3 etc: If the 400 mg bd tablet dose was tolerated, dose escalations would continue each time to Groups 5.2, 5.3 etc. Patient dosing would continue until treatment discontinuation. Dose increases would be at the discretion of the SRC and would continue until the SRC agreed that no further doses should be explored.

CSEP: Group 6: 300 mg bd tablet dose or 400 mg bd tablet dose or 400 mg bd capsule dose until treatment discontinuation.

CSEP: Group 7: The highest bd tablet dose that would have been deemed tolerable by the SRC following the dose escalation phase or 400 mg bd capsule until treatment discontinuation.

CSEP: Group 8: 200 mg tds tablet continuous dosing (Schedule A) or 250 mg tds tablet (intermittent) 2 weeks on study drug, 1 week off study drug (Schedule B) or 400 mg bd tablet (intermittent) 1 week on study drug, 1 week off study drug (Schedule C) or 400 mg od tablet continuous dosing (Schedule D) until treatment discontinuation.

For all patients, regardless of the formulation the patient was treated with or the treatment group assigned to, all patients could receive continuous treatment with the assigned formulation for as long as they remained free from intolerable toxicity and, in the Investigator's opinion, were receiving some clinical benefit from olaparib and did not meet any other discontinuation criteria.

Statistical methods

Statistical methods used in the analyses are described in the statistical analysis plan (SAP). All the listings were programmed using SAS version 9.2.

The primary outcome variable, safety, was based on AEs, physical examination, vital signs including BP pulse and body temperature, ECG and laboratory findings including clinical chemistry, haematology and urinalysis.

Within each cohort in the PK Phase, the PK variables C_{max}, AUC_{0-t} and AUC were analysed statistically using an analysis of variance (ANOVA) model, with factors for patient, formulation (tablet or capsule) and period. All variables were logarithmically transformed prior to analysis. The comparative bioavailability of the tablet compared to the capsule was estimated within each cohort. Corresponding 2-sided 90% CIs were also calculated. These analyses were performed for both dose normalized and non-dose-normalised values. No formal statistical comparisons for the CSEP were performed. The PK parameters for Groups 1-8 are listed and summarised descriptively by formulation and dose.

Formal comparisons of the formulations (i.e. 400 mg bd capsule versus different doses of the tablet within Groups 1 and 6) were performed using an ANCOVA of the percentage change in tumour size at 8 weeks and 16 weeks with covariates for baseline sum of target lesions and treatment arm. A similar ANCOVA was performed for the selected tablet dose schedules in Group 8, taking the 400 mg bd capsule data combined from ovarian cancer patients in Groups 1 and 6 to be used as a comparator. Based on results from the Group 6 analysis, the

300 mg bd tablet dose was also included in the analyses of Group 8 data. In addition to baseline sum of target lesions and treatment arm, the following covariates which are deemed to be prognostic of tumour size were included for the Group 8 analysis: prior platinum chemotherapy status, number of prior chemotherapy regimens and peritoneal involvement at baseline.

The least squares mean difference in percentage change in tumour size was presented along with corresponding 2-sided 80% and 95% CIs, and 2-sided p-values. The 1-sided 80% upper confidence limit for the comparison of tablet versus capsule was used to determine tablet doses and schedules considered to have similar efficacy to the 400 mg bd capsule.

For this analysis, Response Evaluation Criteria in Solid Tumours (RECIST) scans performed within +/-7 days of the protocol scheduled visit were used to determine tumour size. If the visit was not performed within the scheduled time window, the imputation rules (as described within the SAP) were used to impute missing Weeks 8 and 16 data.

Progression-free survival (PFS) by RECIST alone and by RECIST or CA-125 was summarised and presented in Kaplan-Meier plots and compared between the formulation groups using Cox proportional hazards models. Hazard ratios and corresponding 2-sided 80% and 95% CIs were calculated.

Objective response rates (ORRs) by RECIST and by RECIST or CA-125 were compared between formulation groups using logistic regression. Odds ratios and corresponding 2-sided 80% and 95% CIs were calculated using exact methods.

Efficacy analyses have been performed in the overall population of Groups 1, 6 and 8 and in the gBRCA ovarian cancer subgroups of Groups 1 and 6.

Any analysis of the data arising from the exploratory biomarker analysis from Groups 6 and 8 patients have been detailed in a separate exploratory SAP and reported outside of the main CSR.

Subject population

Ten (10) sites in 4 countries (United Kingdom, Switzerland, Belgium and Australia) enrolled and randomised patients into the study. All of these sites enrolled patients into the study (the Australian site 0012 only enrolled into Group 8). The first patient was randomised on 05 November 2008 and the last patient in Group 6 was randomised on 31 August 2011. The data cut-off date (DCO) for the PKP and Groups 1-6 was 24 January 2012. The DCO for Group 8 was 21 August 2013. The disposition of the patients is summarised in Table S3 to Table S6. Group 8 was ongoing at the time of finalisation of the current version of the CSR and was therefore not included in this version.

Overall, the majority of patients were female apart from patients in Cohorts 1-3. The majority of patients were white with no notable differences in demographic characteristics. Patients receiving the 300 mg bd tablet dose in Group 6 had a higher occurrence of current anaemia in their medical history.

Most patients had an ECOG score of 0-1. An ECOG score of 2 was recorded for 1 patient in Groups 1 (200 mg bd tablet), 4 and 5.1 and for 4 patients in Group 6 (2 patients in both the 300 mg bd tablet and 400 mg bd tablet dose levels) but no patients on the 400 mg bd capsule dose levels.

With regards to the overall pathology, a tumour location of breast and ovary were the most common, followed by a tumour location of colorectal. Only patients who were gBRCA ovarian (including primary peritoneal and fallopian tube) cancer patients were included in Group 8. The majority of patients had metastatic disease.

Patients in this study were heavily pre-treated with a median number of 3 or 4 prior regimens of chemotherapy across the groups.

There did not appear to be any difference in compliance between the tablet and capsule doses or cohorts.

There were no important protocol deviations that were likely to have influenced the safety and efficacy conclusions.

Table S3 Summary of patient disposition - PKP/CSP[c]

	Number (%) of Patients		
	Cohort 1	**Cohort 2**	**Cohort 3**
	(Single dose: 50 mg capsule, 25 mg tablet)	**(Single dose: 100 mg capsule, 50 mg tablet)**	**(Single dose:400 mg capsule, 250mg tablet)[d]**
	N=6	**N=6**	**N=6**
Patients enrolled [a]	6	6	6
Patients who received treatment	6 (100.0%)	6 (100.0%)	6 (100.0%)
Patients ongoing at DCO [b]	0	0	1 (16.7%)
Patients who discontinued treatment prior to DCO [b]	6 (100.0%)	6 (100.0%)	5 (83.3%)
Adverse Event	0	0	1 (16.7%)
Condition Under Investigation Worsened	5 (83.3%)	6 (100%)	4 (66.7%)
Unknown [e]	1 (16.7%)	0	0

a Informed consent received.
b Percentages were calculated from number of patients who received treatment.
c CSP was open to all patients who were receiving clinical benefit, were free from intolerable toxicity and met no other discontinuation criteria.
d Dose of tablet decided from Cohort 1 and 2 data.
e Patient E0002002: Reason for discontinuing treatment was unknown.
DCO=Data Cut Off (24 January 2012).

Table S4 Summary of patient disposition - CSEP (Group 2) and the dose escalation phase of the CSEP (Groups 3, 4, 5, 5.1 and 5.2)

	Number (%) of Patients					
	Group 2	**Group 3**	**Group 4**	**Group 5**	**Group 5.1**	**Group 5.2**
	200 mg tablet and 400 mg capsule - crossover[c]	**250 mg bd Tablet**	**300 mg bd Tablet**	**350 mg bd Tablet**	**400 mg bd Tablet**	**450 mg bd Tablet**
	N=9	**N=6**	**N=6**	**N=6**	**N=7**	**N=6**
Patients enrolled [a]	9	6	6	6	7	6
Patients who received treatment	9 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (85.7%)	6 (100%)
Patients ongoing at DCO [b]	0	1 (16.7%)	3 (50%)	1 (16.7%)	0	3 (50%)
Patients who discontinued treatment prior to DCO [b]	9 (100%)	5 (83.3%)	3 (50%)	5 (83.3%)	6 (100%)	3 (50%)
Adverse Event	1 (11.1%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	0
Condition Under Investigation Worsened	7 (77.8%)	4 (66.7%)	2 (33.3%)	3 (50%)	5 (83.3%)	3 (50%)
Unknown [d]	0	0	0	1 (16.7%)	0	0
Voluntary Discontinuation by Subject	1 (11.1%)	0	0	0	0	0

[a] Informed consent received.
[b] Percentages were calculated from number of patients who received treatment.
[c] Used to directly compare steady state PK of capsule and tablet.
[d] Patient E0002017: Unknown reason for discontinuing study treatment; discontinuation of study due to death.

DCO=Data Cut Off (24 January 2012).

Table S5 Summary of patient disposition - CSEP (Group 1) and the dose escalation phase of the CSEP (Group 6) - All patients

	Number (%) of Patients				
	Group 1		Group 6		
	200 mg bd Tablet	400 mg bd Capsule	300 mg bd Tablet	400 mg bd Tablet	400 mg bd Capsule
	N=13	N=11	N=18	N=17	N=18
Patients enrolled [a]	13	11			
Patients randomised	13 (100%)	11 (100%)	18 (100%)	17 (100%)	18 (100%)
Patients who received treatment	13 (100%)	11 (100%)	18 (100%)	17 (100%)	18 (100%)
Patients ongoing at DCO [b]	2 (15.4%)	0	7 (38.9%)	6 (35.3%)	10 (55.6%)
Patients who discontinued treatment prior to DCO [b]	11 (84.6%)	11 (100%)	11 (61.1%)	11 (64.7%)	8 (44.4%)
Condition Under Investigation Worsened	10 (76.9%)	9 (81.8%)	8 (44.4%)	9 (52.9%)	8 (44.4%)
Unknown [c]	0	0	1 (5.6%)	1 (5.9%)	0
Other - Patient no longer receiving clinical benefit from study drug	0	1 (9.1%)		0	0
Other – Symptomatic deterioration	0	0	1 (5.6%)	0	0
Other – Liver function tests not compatible with ongoing therapy	0	0	1 (5.6%)	0	0
Subject Decision	0	0	0	1 (5.9%)	0
Subject Lost to Follow-up	1 (7.7%)	1 (9.1%)	0	0	0

[a] Informed consent received.
[b] Percentages were calculated from number of patients who received treatment.
[c] Group 6 (300 mg bd tablet): Patient E0003017: Unknown reason for discontinuing study treatment; discontinuation of study due to
Group 6 (400 mg bd tablet): Patient E0007009: Unknown reason for discontinuing study treatment; discontinuation of study due to death.

DCO=Data Cut Off (24 January 2012).

Table S6 Summary of patient disposition - Randomised tablet formulation (CSEP) (Group 8)

	Number (%) of Patients			
	Group 8			
	200 mg Tablet tds Cont	**250 mg Tablet tds Inter**	**400 mg Tablet bd Inter**	**400 mg Tablet od Cont**
	N=16	**N=15**	**N=16**	**N=15**
Patients enrolled [a]	16	15	16	15
Patients randomised	16 (100.0%)	15 (100.0%)	16 (100.0%)	15 (100.0%)
Patients who received treatment	16 (100.0%)	15 (100.0%)	16 (100.0%)	15 (100.0%)
Patients ongoing at DCO [b]	3 (18.8%)	4 (26.7%)	6 (37.5%)	4 (26.7%)
Patients who discontinued treatment prior to DCO [b]	13 (81.3%)	11 (73.3%)	10 (62.5%)	11 (73.3%)
Adverse Event	0	1 (6.7%)	0	1 (6.7%)
Condition Under Investigation Worsened	12 (75.0%)	10 (66.7%)	9 (56.3%)	10 (66.7%)
Subject decision	1 (6.3%)	0	1 (6.3%)	0

[a] Informed consent received.
[b] Percentages were calculated from number of patients who received treatment.
DCO=Data Cut Off (21 August 2013).
Cont=Continuous dosing schedule; Inter=Intermittent dosing schedule.

Summary of efficacy results

Continued Supply Expansion Phase (CSEP): Group 1

A numerically higher but non-statistically significant difference in percentage change in tumour size from baseline was observed in patients who received the 400 mg bd capsule dose compared to patients who received the 200 mg bd tablet dose, in both the overall population and in the subset of ovarian cancer patients;

- Overall population: 200 mg bd tablet – 400 mg bd capsule difference in LS Means at Week 8=14.7%, 95% CI: -15.4%, 44.9%; p=0.320.
- Ovarian cancer population: 200 mg bd tablet – 400 mg bd capsule difference in LS Means at Week 8=8.6%, 95% CI: -22.5%, 39.8%; p=0.557.

Three (3) patients experienced an objective response: 2 (18.2%) out of 11 patients who received the 400 mg bd capsule dose (1 ovarian patient) and 1 (7.7%) out of 13 patients who received the 200 mg bd tablet dose.

Dose escalation phase of the Continued Supply Expansion Phase (CSEP) (Group 6) and randomised tablet formulation (CSEP) (Group 8)

In both the full analysis set and the ovarian cancer subset, a decrease was observed in mean tumour size in patients who received the 400 mg bd capsule dose at Weeks 8 and 16 compared to baseline. There was also evidence of a decrease in mean tumour size at Weeks 8 and 16 in patients who received the tablet formulation (300 mg and 400 mg dose).

No statistically significant differences in change in tumour size were observed between the Group 6 tablet doses and 400 mg bd capsule dose;

- In the overall population 300 mg bd tablet comparison, the difference was numerically in favour of 400 mg bd capsule; Week 8 difference=11.0%, 95% CI: -9.0%, 31.0%; p=0.275.

- In the ovarian cancer population 300 mg bd tablet comparison, the two treatments were similar; Week 8 difference=1.8%, 95% CI: -22.8%, 26.4%; p=0.881.

- In the overall population 400 mg bd tablet comparison, the difference was numerically in favour of the 400 mg bd tablet; Week 8 difference= -8.0%, 95% CI: -28.3%, 12.3%; p=0.430. Consistent results were seen in the ovarian cancer population.

An objective response was achieved by 6 (33.3%) out of the 18 patients who received the 300 mg bd tablet dose (5 of which were ovarian cancer patients), 5 (29.4%) out of 17 patients who received the 400 mg bd tablet dose (5 of which were ovarian cancer patients) and 7 (38.9%) out of 18 patients who received the 400 mg bd capsule dose (5 of which were ovarian cancer patients).

- Following assessment of the 1 sided 80% UCL for the difference in LS mean change in tumour size at Week 8 in ovarian cancer patients across all doses it was concluded the 300 mg bd and 400 mg bd tablet doses had similar efficacy to the 400 mg bd capsule dose.

Summary of pharmacokinetic results

Relative bioavailability phase

Following oral doses of the capsule formulation, the plasma concentration –time profiles at all doses were well characterised with <15% of the AUC extrapolated beyond the last data point. Mean apparent clearance appeared to be faster and mean apparent volume of distribution greater at the 400 mg dose level than at the two lower doses perhaps indicating a reduction in bioavailability at this higher dose. Exposure increased approximately proportionally with dose

between the 50 and 100 mg doses but less than proportionally thereafter with gmean C_{max} increasing 1.6 and 3.1-fold and gmean AUC increasing 1.7 and 5.8-fold respectively for a 2 and 8-fold increase in administered dose.

Following oral doses of the tablet formulation, the absorption of olaparib was slightly more rapid than seen for the capsule, with maximum plasma concentrations typically observed between 0.5 and 2 hours after dosing. Following the peak, the plasma concentration time profiles at all dose levels declined biphasically with a terminal half life of between approximately 5 and 9 hours and no evidence of any change in half life with increasing dose. The mean apparent plasma clearance and volume of distribution was 5.42 L/h (± 2.60 SD) and 54.9 L (± 30.1 SD). Exposure increased approximately proportionally with dose with gmean C_{max} increasing 1.9 and 7.5-fold and gmean AUC increasing 1.6 and 12.2-fold for a 2 and 10-fold increase in administered dose.

Although not powered as a bioequivalence study, on the basis of the calculated glsmean Cmax and AUC ratios and 90% CIs obtained in these cohorts, the tablet and the capsule formulations cannot be considered bioequivalent.

Dose escalation phase

Within a dose level, C_{max} and AUC_{0-12} following the first dose of the study and $C_{max,ss}$ and AUC_{ss} on Day 29 of dosing typically spanned a 2 to 4-fold range. In general, with the exception of the 300 mg bd cohort data, exposure following the first dose of the study increased with increasing dose. In view of the variability in the data, particularly in the 350 mg bd and 400 mg bd cohorts, it is difficult to draw such conclusions from the Day 29 data.

Efficacy expansion phase

Data obtained following dosing of the 200 mg bd tablet dose to cohorts of genetic breast cancer gene patients showed that the tablet dose did deliver exposures which fell within the range of the capsule values, although the average C_{max} was higher (6.88 µg/mL vs 5.70 µg/mL) and both the average $AUC_{0\ 12}$ and C_{min} were lower (36.1 µg.h/mL vs 43.1 µg.h/mL and 1.00 µg/mL vs 1.86 µg/mL, respectively) than achieved in a separate cohort of patients following the 400 mg bd capsule dose. However steady state data generated from a further cohort of patients (Group 2) randomised to bd dosing with both the 200 mg bd tablet and the 400 mg bd capsule dose (N=6), demonstrated that the 2 formulations could not be concluded to be bioequivalent. Although gmean $C_{max,ss}$ was similar (8.02 vs 8.10 µg/mL) following the tablet and capsule doses, gmean AUC_{ss} was approximately 20% lower (38.4 vs 48.5 µg.h/mL) and gmean $C_{min,ss}$ approximately 50% lower (0.68 vs 1.38 µg/mL) following the tablet dose.

PK data obtained from the patients in Group 6 indicates that following both single and multiple dosing at the 300 mg bd and 400 mg bd tablet doses, the exposures achieved were consistently higher than those achieved following the 400 mg bd capsule dose.

Efficacy expansion phase: Randomised tablet formulations

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Following multiple dosing of the tablet formulation, all dosing schedules tested except the 400 mg once daily schedule, delivered mean steady state C_{max}, steady state C_{min} and daily AUC which exceeded those achieved following the 400 mg bd capsule dose. Examination of the calculated cumulative AUCs that would be expected (assuming adequate tolerability) to be delivered by the various dosing schedules over 2, 3 and 4 weeks of dosing showed that only the 200 mg tds, 300 mg bd and 400 mg bd dosing regimens consistently delivered exposures that matched/exceeded that delivered by the 400 mg bd capsule dose over those periods.

Assessment of the effect of food on the exposure of olaparib melt-extrusion (tablet) formulation

A preliminary investigation of the effect of food (light meal) was performed in the patients dosed in the 400 mg od cohort. Although slightly confounded by the small amount of accumulation which would be expected to occur on once daily multiple dosing of olaparib via the tablet formulation (~10% based on the average $t_{½}$ of ~7 hours), the treatment ratios (fed:fasted) and 90% CI for C_{max} and AUC_{0-24} were, respectively, 1.13 (1.00, 1.27) and 1.15 (1.01 to 1.31) thus showing no major impact of a light breakfast on either exposure parameter for the tablet formulation.

Summary of pharmacodynamic results

To compare the extent of poly (ADP-ribose) polymerase (PARP) inhibition achieved in peripheral blood mononuclear cells (PBMCs) following dosing of both the tablet and capsule formulation, PBMC samples were obtained from the 18 patients dosed in the PKP phase only. The PARP inhibition data showed high variability and an average extent of inhibition from baseline which generally fell between 20 and 80%. Although interpretation of these data is highly confounded by the extent of variability in it, there was no clear evidence of any dose response in the extent of PARP inhibition observed and no evidence of a difference in the extent of inhibition achieved after dosing the two formulations. Inhibition of PARP-1 seemed, in general to be greatest at the 10 hour post dose time-point and appeared to show some degree of recovery by 24 hours after dosing. The variability in the data appeared to be greater following the capsule formulation doses than seen following the tablet.

Summary of safety results

For the PKP, the duration of exposure was only calculated for patients who started the CSP (400 mg bd capsule); the actual treatment duration (median) (that excluded dose interruptions) was 87 days (range: 6-1074 days). For Group 2 (CSEP), the duration of exposure was only calculated for patients who entered the continuous dosing (200 mg bd tablet); the actual treatment duration (median) (that excluded dose interruptions) was 42 days (range: 27-230 days). For Group 3 (250 mg bd tablet), Group 4 (300 mg bd tablet), Group 5 (350 mg bd tablet), Group 5.1 (400 mg bd tablet) and Group 5.2 (450 mg bd tablet) the actual treatment durations (median) (that excluded dose interruptions) were 250 days (range: 22-551 days), 327 days (range: 50-491 days), 116 days (8-380 days), 111 days (range: 44-196 days) and

207 days (57-240 days) respectively. For the 200 mg bd tablet and 400 mg bd capsule of Group 1, the actual treatment durations (median) (that excluded dose interruptions) were 114 days (range: 30-844 days) and 193 days (range: 34-416 days) respectively. For the 300 mg bd tablet, the 400 mg bd tablet and the 400 mg bd capsule of Group 6, the actual treatment durations (median) (that excluded dose interruptions) were 135 days (range: 56-281 days), 166 days (range: 17-281 days) and 178 days (range: 62-277 days) respectively. For the 200 mg tds tablet, the 250 mg tds tablet (intermittent), the 400 mg bd tablet (intermittent) and the 400 mg od tablet of Group 8, the actual treatment durations (median) (that excluded dose interruptions) were 164 days (range: 4-390 days), 221 days (range: 5-413 days), 271 days (58-366 days) and 211 days (range: 26-463 days) respectively.

Adverse events were commonly reported in all dose levels with those most frequently reported being consistent with the known safety profile of olaparib, namely nausea, vomiting, fatigue and anaemia. AEs with a CTCAE Grade 3 or higher included anaemia, fatigue, vomiting, neutropenia and nausea. The reported frequency and severity of these common adverse events was generally higher in the 400 mg bd tablet dose level. Whilst the nausea, vomiting and fatigue were generally low grade (CTCAE Grades 1 and 2), anaemia was reported as CTCAE Grade 3 or higher in 22% of patients in the 300 mg bd tablet dose level (1 patient [5.6%] had a SAE of anaemia), in 22% of the patients in the 400 mg bd capsule dose level (1 patient [5.6%] had a SAE of anaemia) and in 29% of the patients in the 400 mg bd tablet dose level (5 [29.4%] patients had a SAEs of anaemia).

Group 5.1 (400 mg bd tablet) had the highest percentage of patients (83.3%) with an AE of a CTCAE Grade 3 or higher.

The overall number of patients with AEs leading to permanent discontinuation of the study drug were low.

Dose reductions were more frequent at higher tablet doses with Group 5.2 (450 mg bd tablet dose) having the highest percentage of patients (83.3%) who had one or more dose reductions which was followed by 64.7% of patients who received the 400 mg bd tablet dose in Group 6. The percentage of patients with one or more dose reductions was comparable for the 300 mg bd, 200 mg tds, and 400 mg bd (intermittent) dose levels (22.2%, 25.0% and 37.5%, respectively), and lower at the 250 mg tds (intermittent) and 400 mg od dose levels (both 13.3%). All dose reductions were due to AEs.

The number of patients who reported SAEs (including AEs with an outcome of death) was similar across most of the treatments ranging from 15.4% to 41.2%. The 400 mg bd tablet dose of Group 6 had the highest percentage of patients who reported SAEs (including AEs with an outcome of death) (7 patients [41.2%]) of which 2 patients [11.8%] had more than 1 SAE.

There were 7 deaths across all groups during the dosing period. There were 4 deaths related to the disease under investigation (ovarian cancer) only: 1 ovarian cancer patient (Group 1 400 mg bd capsule dose) and 1 ovarian cancer patient (Group 4 300 mg bd tablet) and 2 patients in the 400 mg od tablet dose level of Group 8. There were 3 deaths due to disease

under investigation and an AE. One (1) patient in Group 5 (350 mg bd tablet) died of ovarian cancer and pneumocystis carinii pneumonia which was assessed by the investigator to be causally related to the study drug and occurred 1 day after treatment discontinuation (03 March 2011) (event start date: 04 March 2011; date of death: 16 March 2011). One (1) patient in Group 6 (400 mg bd tablet) died of metastatic breast cancer and intra-abdominal haemorrhage which was assessed by the investigator not to be causally related to the study drug. One (1) patient in Group 8 (400 mg od tablet) died of locally advanced ovarian cancer and small intestinal obstruction, which was assessed by the investigator not to be causally related to the study drug.

There were no new findings in any of the clinical laboratory, vital signs or physical examination safety parameters and no individual abnormalities raised any new safety concerns considering the known safety profile of the study drug.

The number of patients who received at least one blood transfusion during the study was highest in the 400 mg bd tablet dose level (64.7%; this included 1 patient who received 2 platelet transfusions) compared to the 300 mg bd tablet (38.9%) and 400 mg bd capsule (33.3%). Of note, more patients in the 300 mg bd tablet dose level (haemoglobin range at baseline: 91.0-134.0 g/L) had a current medical history at study entry of anaemia (6 patients) than any of the other groups (3 patients in the 400 mg bd tablet dose level [haemoglobin range at baseline: 97.0-144.0 g/L] [Group 6], 2 patients in the 400 mg bd capsule dose level [haemoglobin range at baseline: 107.0-144.0 g/L] [Group 1] and no patients 400 mg bd capsule dose level [Group 6]) potentially confounding the on treatment assessment of anaemia in the 300 mg bd tablet dose level. The inclusion criteria for all groups apart from Group 8 required a patient to have a haemoglobin level of ≥9.0 g/dL at study entry. Prior to the recruitment into Group 8, the inclusion criteria was amended to a haemoglobin level of ≥10.0 g/dL and patients were not allowed to have received blood transfusions in the 4 weeks prior to randomisation. In Group 8, fewer patients overall reported anaemia or required blood transfusions.

Following the expansion phase, the 450 mg bd tablet dose (Group 5.2) was considered less well tolerated and deemed unsuitable for further study due to unacceptable haematological toxicity and high number of dose modifications.