

An adaptive study to determine the optimal dose of the tablet formulation of the PARP inhibitor olaparib

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ABSTRACT

Background: Olaparib is poorly soluble, requiring advanced drug delivery technologies for adequate bioavailability. Sixteen capsules/day are required for the approved 400 mg twice daily dose; a tablet formulation was developed to reduce pill burden. This clinical trial evaluated the optimal dose and administration schedule of the tablet formulation.

Patients and methods: Two stages of sequentially enrolled cohorts: stage 1, pharmacokinetic properties of tablet and capsule formulations were compared in patients with advanced solid tumours; stage 2, tablet dose escalation with expansion cohorts at doses/schedules of interest in patients with solid tumours and *BRCAm* breast/ovarian cancers.

Results: Olaparib 200 mg tablet displayed similar $C_{max,ss}$ but lower AUC_{ss} and $C_{min,ss}$ than 400 mg capsule. Following multiple dosing, steady-state exposure with tablet ≥ 300 mg matched or exceeded that of 400 mg capsule. After dose escalation, while 400 mg twice daily was the tablet maximum tolerated dose based on haematological toxicity, 65% of patients in the randomized expansion phase eventually required dose reduction to 300 mg. Intermittent tablet administration did not significantly improve tolerability. Tumour shrinkage was similar for 300 and 400 mg tablet and 400 mg capsule cohorts.

Conclusions: The recommended monotherapy dose of olaparib tablet for Phase III trials was 300 mg twice daily, simplifying drug administration from 16 capsules to four tablets per day.

Clinical trial number: NCT00777582 (ClinicalTrials.gov)

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KEY POINTS

- An alternative tablet formulation of the PARP inhibitor olaparib with improved bioavailability has been developed to facilitate olaparib administration to patients.
- Following multiple dosing, steady-state exposure with olaparib tablet ≥ 300 mg matched or exceeded that of the olaparib 400 mg capsule.
- Efficacy in relation to tumour shrinkage was similar between olaparib 300 and 400 mg tablet and 400 mg capsule doses; owing to haematological toxicity, tolerability was improved with olaparib 300 mg BD tablet formulation.
- The recommended monotherapy dose of olaparib tablet for Phase III trials was 300 mg twice daily, simplifying drug administration from 16 capsules to four tablets per day.

1 INTRODUCTION

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3 Poly(ADP-ribose) polymerases (PARPs) play a key role in detecting DNA damage and
4 triggering activation of DNA repair pathways. Two seminal publications laid the
5 foundation for clinical development of PARP inhibitors in the treatment of cancers
6 harbouring a *BRCA1/2* mutation [1, 2]. Individuals carrying *BRCA* mutations (*BRCAm*)
7 account for 15% of cases of high-grade serous ovarian carcinoma [3, 4] and 10–20% of
8 cases of triple-negative breast cancer (oestrogen-receptor-, progesterone-receptor-, and
9 HER2-negative tumours) [5, 6].

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11 A proof-of-concept clinical trial of olaparib (Lynparza™), a potent oral inhibitor of PARP1
12 and PARP2, established 400 mg capsule (CAP) formulation twice daily (BD) as the
13 maximum tolerated dose (MTD) [7]. Drug exposure increased proportionally with doses
14 up to 100 mg BD, with less-marked increases above this threshold, and
15 pharmacodynamic (PD) effects plateaued at doses >60 mg BD. However, further clinical
16 trials in breast and ovarian *BRCAm* cancer suggested a dose–response relationship,
17 supporting use of the MTD of olaparib over a minimal biologically effective dose [8-10].

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19 Subsequent Phase II studies of olaparib confirmed the sustained antitumour activity in
20 patients with germline *BRCAm* (*gBRCAm*) high-grade serous epithelial ovarian [8, 10],
21 breast and other tumour types [9, 11]; olaparib antitumour activity was also observed in
22 sporadic cancers [12]. ‘*BRCAness*’ is used to refer to tumours with *BRCA*-like genomic
23 or post-transcriptional aberrations, suggesting a wider application of PARP inhibitors [13-
24 15] beyond tumours associated with *BRCAm*. In a randomized Phase II study in patients
25 with platinum-sensitive recurrent ovarian cancer, olaparib maintenance therapy
26 improved progression-free survival (PFS) and patients with *BRCAm* were most likely to
27 benefit from treatment [16, 17]. In December 2014, the CAP formulation of olaparib
28 received EU [18] and US [19] approval. To receive the approved 400 mg BD CAP dose,
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1 patients need to take 8x50 mg large size 0 capsules twice daily. To improve dosing
2 constraints of the CAP formulation, a melt-extrusion tablet (TAB) formulation with
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4 improved bioavailability was developed.
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7 We report results of an open-label, multicentre, multistage, Phase I trial comparing the
8 pharmacokinetics (PK), efficacy and tolerability of different doses and scheduling of the
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10 olaparib CAP and TAB formulations to determine an optimal TAB dosing strategy for
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Phase III studies of olaparib.

2 PATIENTS AND METHODS

2.1 Study design

The Phase I study was conducted in two sequential stages (Online Resource 1, Supplementary Figure 1; ClinicalTrials.gov NCT00777582): stage 1 was a randomized, two-period, crossover design to determine the comparative bioavailability of the two formulations (bioavailability assessment; patients could then enter a continued-supply phase [CSP; cohorts 1–3]) followed by a dose-expansion phase (groups 1–2) to validate PK modelling and determine steady-state PK; stage 2 determined the MTD and optimum schedule of the TAB formulation (using dose-escalation [groups 3–5.2] and dose-expansion, randomized TAB/CAP comparison [group 6]; dose-expansion, randomized TAB alternative dosing schedules, group 8).

Institutional review boards/independent ethics committees of the 10 investigational sites approved the protocol. All patients provided written informed consent. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice and the AstraZeneca policy on bioethics [20].

2.1.1 Stage 1 – bioavailability assessment

Patients were randomized to two treatment periods of olaparib CAP and TAB, separated by a 6- to 14-day washout, to study the PK profile at different dose levels (Online Resource 1, Supplementary Figure 1). On completion, patients could enter a CSP, where they received olaparib 400 mg BD CAP until disease progression, unacceptable toxicity or withdrawal of consent. Based on an estimate of intra-subject variability following CAP dosing, a sample size of six patients for each dose level was expected to produce a 90% confidence interval (CI) of 1.61–2.49 for the comparative bioavailability assessment. PK modelling and simulation was performed to select a TAB dose expected

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2 to have comparable steady-state maximum plasma concentration (C_{max}) and area under
3 the plasma concentration–time curve (AUC) to the 400 mg BD CAP dose.
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6 Once the TAB dose was determined, a dose-expansion phase was initiated to validate
7 PK modelling for the selected TAB and 400 mg BD CAP (group 1). A second group of
8 six patients (group 2) was randomly assigned to one of two treatment sequences:
9 selected TAB dose BD days 1–8 followed by 400 mg BD CAP days 9–15 or vice versa.
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11 After day 15, all patients received selected TAB until treatment discontinuation.
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18 Primary objectives of stage 1 were to determine comparative bioavailability of the TAB
19 and CAP formulations and to assess safety and tolerability (group 1). Secondary
20 objectives were to: generate single-dose PK data and information on dose linearity of
21 the TAB formulation; assess preliminary efficacy of the TAB and CAP formulations
22 (group 1); compare steady-state exposure achieved with selected TAB and 400 mg BD
23 CAP (group 2).
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32 33 **2.1.2 Stage 2 – dose-schedule optimization** 34 35

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37 Stage 1 data indicated that higher TAB doses should be explored. The protocol was
38 amended to include a second stage with a rolling dose-escalation design (groups 3–5.2).
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40 The MTD was defined as the maximum dose at which $\geq 33\%$ of patients experienced
41 dose-limiting toxicities (DLTs).
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47 Following completion of dose escalation, a randomized safety and efficacy comparison
48 between the selected TAB dose levels and the original CAP regimen was conducted in
49 patients with *gBRCAm* breast or ovarian cancer (group 6).
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55 To assess tolerability and scheduling of the higher daily doses, the protocol was
56 amended to recruit patients with *gBRCAm* ovarian cancer in a further randomized group
57 using alternative TAB schedules (group 8). Patients were randomized 1:1:1:1 to:
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schedule A, 200 mg three times daily (TID); schedule B, 250 mg TID 2 weeks on, 1 week off; schedule C, 400 mg BD 1 week on, 1 week off; or schedule D, 400 mg once daily (QD).

Primary objectives of stage 2 were to: determine safety and tolerability profile of doses higher than 200 mg BD TAB (groups 3–5.2); compare safety of higher TAB doses with 400 mg CAP dose in *gBRCAm* breast or ovarian cancer patients (group 6); and determine safety and tolerability of alternative TAB schedules in *gBRCAm* breast or ovarian cancer patients (group 8). Secondary objectives were to: determine single-dose and steady-state exposures with higher doses and selected schedules of TAB (groups 3–5, 8); compare single-dose and steady-state exposures of TAB with 400 mg CAP; and assess efficacy in patients treated with TAB or CAP (groups 6, 8).

2.2 Patients

Key patient eligibility criteria were: age ≥ 18 years; advanced solid tumours with no effective treatment available; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; adequate bone marrow (haemoglobin ≥ 9.0 g/dL, platelet count $\geq 100 \times 10^9/L$, white blood cells $> 3 \times 10^9/L$), renal (serum creatinine $\leq 1.5 \times$ upper limit of normal [ULN]), and hepatic (total bilirubin $\leq 1.5 \times$ ULN; aspartate transaminase [AST]/alanine transaminase [ALT] $\leq 2.5 \times$ ULN, unless liver metastases present, in which case $\leq 5 \times$ ULN) function; eligibility criteria are detailed in Online Resource 1, Supplementary Table 1. After protocol amendments, group 8 required ECOG PS 0–1 and baseline haemoglobin ≥ 10 g/dL, independent of blood transfusion, within 4 weeks of randomization.

Only patients with *gBRCAm* breast or ovarian cancer were recruited into groups 1 and 6. Group 8 was limited to *gBRCAm* patients with ovarian, primary peritoneal or fallopian tube cancer. These groups were required to have at least one measurable lesion.

2.3 Study endpoints and assessments

Assessments included medical review, physical examination, vital signs, and clinical laboratory tests and were performed weekly during the first 4 weeks and 4-weekly thereafter. Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0. DLT was defined as any of the following AEs occurring in the first 28 days of treatment and judged by the investigators to be related to olaparib: grade (G) 4 neutropenia lasting >5 days or associated with fever; G4 thrombocytopenia; G \geq 2 cardiac or neurological toxicity; any AE that delayed the start of course 2 for >14 days from the planned date; or other G3–4 events, except fatigue, nausea and vomiting, diarrhoea, myalgia or arthralgia, unless appropriate prophylactic/therapeutic measures have been administered. Guidelines for management of common toxicities were implemented at investigational sites, including uniform rules for dose modifications. Radiological assessments were performed every 8 weeks according to Response Criteria in Solid Tumors (RECIST) v1.0. Tumour shrinkage, objective response rate (ORR) and response rate in ovarian cancer were based on CA-125 (GCIG) and RECIST [21, 22].

2.4 Pharmacokinetics and modelling analysis

Blood samples were collected at pre-specified times during stages 1 and 2 of the study. Primary outcome variables to determine the comparative bioavailability of the TAB and CAP formulations were single-dose C_{max} , AUC and AUC to time t (AUC_{0-t}). Single-dose PK parameters of time to maximum plasma concentration (t_{max}), oral clearance (CL/F), terminal half-life ($t_{1/2}$) and volume of distribution (V_{area}/F) were also determined. Multiple-dose PK parameters for groups 1, 2 and 3–8 of the dose-escalation phase and the randomized TAB formulations included assessment of AUC_{ss} , $C_{max,ss}$ and $C_{min,ss}$.

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PK parameters for the comparative bioavailability phase and group 2 CAP/TAB crossover phase were generated using standard non-compartmental analysis. PK data from the bioavailability assessment cohorts were used to build a population PK model for olaparib by fitting a two-compartment model with first-order absorption, first-order elimination and a lag time to the data. The population parameter and inter-individual variability estimates obtained from this model were used to predict the TAB dose, with expected steady-state plasma exposures within the range of those observed following dosing of the 400 mg BD CAP dose by simulating multiple-dose PK parameters ($C_{max,ss}$, AUC_{ss}) following administration of the TAB formulation at 1–250 mg BD doses for a patient population of 10,000. The $C_{max,ss}$ and $AUC_{0-12,ss}$ values obtained were compared with previously determined ranges following 400 mg BD CAP dosing, and the percentage of patients with values within these ranges was determined for each TAB dose. The chosen TAB dose for groups 1 and 2 was predicted to provide a $C_{max,ss}$ and AUC_{ss} within the 400 mg CAP range for these parameters in 95% of patients. In group 1 and in stage 2 (groups 3–8), $C_{max,ss}$, $C_{min,ss}$ and AUC_{ss} at different doses and schedules of TAB were determined following sparse PK sampling and analysed using the same population PK model.

2.5 Pharmacodynamics

Methodology and results of the PD analysis are provided in Online Resource 1, Supplementary Table 2.

2.6 Statistical analysis

The extent of exposure, AEs, DLTs and percentage inhibition of PARP in peripheral blood mononuclear cells were summarized with descriptive statistics. Single-dose PK, linearity, and comparative bioavailability were assessed in stage 1.

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In stage 1, plasma concentration data and PK and PD parameters were summarized descriptively by dose level and formulation administered. Within each cohort, comparative bioavailability and 90% CIs were estimated using analysis of variance with factors for patient, formulation and period.

A planned comparison of the preliminary data on antitumour activity in patients with ovarian cancer in groups 1, 6 and 8 was conducted, based on analysis of covariance (ANCOVA) of the percentage change in tumour size after 8 and 16 weeks of treatment, using comparator data from all ovarian cancer patients receiving the CAP formulation. The ANCOVA models were adjusted for baseline tumour size and, additionally for group 8, prior platinum chemotherapy status (with categories for resistant, sensitive and no prior platinum use/unknown) [23], number of prior chemotherapy regimens (discrete variable) and peritoneal involvement at baseline (as a dichotomous variable); the latter two variables were identified as possible prognostic factors based on exploratory analysis of data from the olaparib clinical programme.

Ruling out a 20% difference (based on <20% one-sided 80% upper confidence limit [UCL]) was used as a definition of non-inferiority for a given TAB dose compared with the 400 mg BD CAP formulation. This difference was based on Phase II studies comparing 100 and 400 mg CAP-based doses [8, 9].

3 RESULTS

3.1 Patient characteristics

Between 2008 and 2012, 210 patients (87% female) enrolled in the study and 196 received olaparib. Fifty-one patients enrolled in stage 1 and 159 in stage 2, including 31 in the dose-escalation phase. Patient characteristics are detailed in Table 1; all patients had metastatic or locally advanced non-resectable disease at enrolment.

3.1.1 Stage 1

Ovarian, breast and colorectal cancers were the most common tumour types (Table 1). Median time on treatment was 87 days for patients in the PK phase (PKP)/CSP (cohorts 1–3).

3.1.2 Stage 2

Patients in the dose-escalation (groups 3–5.2; $n=31$) and dose-expansion phase of stage 2 (groups 6 and 8; $n=115$) had ovarian ($n=114$) or breast ($n=27$) cancer, with the exception of five patients ($n=1$ each; metastatic castration-resistant prostate cancer, gastric cancer, uterine leiomyosarcoma, renal cell carcinoma, oesophageal-gastric junction carcinoma). Sixty-two *gBRCAm* patients with ovarian, primary peritoneal or fallopian tube cancer were randomized to receive the four alternative TAB schedules (group 8). Patients in groups 6 and 8 had confirmed *gBRCAm*; *gBRCAm* status for groups 1, 6 and 8 are reported in Online Resource 1, Supplementary Table 3.

Overall, 137 patients with serous (all grades) ovarian carcinoma, including primary peritoneal and fallopian tube adenocarcinoma, received olaparib. Platinum sensitivity status was available for patients in groups 6 and 8, of which 40/100 patients (40%) had platinum-sensitive disease, assessed by the investigator, at study entry. The median

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number of prior lines of chemotherapy ranged from two to six across cohorts and groups.

3.2 Bioavailability assessment

Following PK analysis for single doses of 25 and 50 mg TAB in cohorts 1 and 2, a 250 mg dose was selected for cohort 3, assuming dose proportionality would occur at TAB doses >50 mg and exposures would not exceed those previously achieved following ≤600 mg CAP [7].

In all three cohorts (1–3; Figure 1 and Online Resource 1, Supplementary Table 4), absorption was rapid, with maximum concentrations observed 0.5–2 hours after TAB dosing (compared with 1–3 hours for CAP [50, 100 and 400 mg doses]). Following this peak, plasma concentration–time profiles declined biphasically, with a $t_{1/2}$ of 5–9 hours and no change in $t_{1/2}$ with increasing dose. The overall mean $t_{1/2}$ for TAB was 6.97 hours (standard deviation [SD] 1.06 hours). The mean (SD) CL/F and V_{area}/F was 5.42 (2.60) L/h and 54.9 (30.1) L, respectively. Exposure increased approximately dose proportionally, with geometric mean (gmean) C_{max} increasing 1.9- and 7.5-fold, and gmean AUC increasing 1.6- and 12.2-fold, respectively, for a two- and 10-fold dose increase.

The relative bioavailability of TAB doses compared with CAP was higher based on C_{max} ; however, AUC values were similar at the two lower TAB doses (Online Resource 1, Supplementary Table 4). Exposure following CAP dosing increased less than proportionally at doses >100 mg, and both C_{max} and AUC values were higher with 250 mg TAB than with the comparative CAP dose (400 mg). Based on geometric least squares mean (gLSmean) C_{max} and AUC ratios and 90% CIs from the 18 patients in these three cohorts, the TAB and CAP formulations cannot be considered bioequivalent.

1 Further PK modelling and simulation of data predicted that a 200 mg BD TAB dose
2 would deliver steady-state C_{max} and AUC_{0-12} values within the range observed for
3 patients receiving 400 mg BD CAP. To validate these modelling results, six additional
4 patients received 200 mg TAB and 400 mg CAP in a crossover design (group 2).
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6 Although gmean $C_{max,ss}$ was similar, gmean AUC_{ss} was ~20% lower and gmean $C_{min,ss}$
7 ~50% lower following 200 mg TAB versus 400 mg CAP (Online Resource 1,
8 Supplementary Table 4). Further assessment of steady-state PK was conducted during
9 stage 2; gmean $C_{max,ss}$, $C_{min,ss}$ and $AUC_{0-12,ss}$ with 300 and 400 mg TAB BD in the
10 expansion cohorts exceeded those achieved with the 400 mg BD CAP dose (Table 2).
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22 **3.3 Safety and tolerability**

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25 Tables 3 (dose-expansion and dose-escalation cohorts) and 4 (expansion phase,
26 alternative dosing schedule cohorts) list the median exposure to olaparib, the most
27 commonly reported AEs (Table 4 only) and $G \geq 3$ AEs. Online Resource 1,
28 Supplementary Table 5 details the most commonly reported AEs for the dose-expansion
29 and dose-escalation cohorts, and Online Resource 1, Supplementary Table 6
30 summarizes haemoglobin toxicity for groups 6 and 8.
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40 During TAB dose escalation, the 450 mg BD dose level was deemed non-tolerable; G3
41 anaemia, thrombocytopenia and neutropenia occurred in 3/6 (50%), 1/6 (17%) and 1/6
42 patients (17%), respectively; overall, 5/6 patients (83%) required a dose reduction
43 because of drug-related AEs. The 400 mg BD TAB dose was defined as the MTD for
44 additional expansion cohorts.
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52 Nausea and vomiting were the most commonly reported AEs in the dose-expansion and
53 dose-escalation phases (reported in 84% [nausea] and 80% [vomiting] of patients in
54 groups 1 and 3–6); in these groups, 8% and 1% of patients had a dose reduction
55 because of nausea and vomiting, respectively. The incidence of G3–4 anaemia and
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1 thrombocytopenia was higher in the 400 mg BD group than the 300 mg BD group (30%
2 vs 22% and 18% vs 0%, respectively).
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5 In 18 patients randomized to the approved 400 mg BD CAP regimen (group 6), anaemia
6 was reported for 6/18 patients (33%; including four cases of G \geq 3 anaemia [22%]; G1–2
7 nausea occurred in 15/18 cases [83%] and vomiting in 5/18 patients [28%], including
8 one G3 [5.6%]).
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16 Eight patients in the dose-expansion phase required permanent discontinuation of
17 olaparib because of an AE across dose levels ($n=1$ patient each: nausea; vomiting; rash;
18 increased AST; increased ALT; small intestinal obstruction; myalgia and rash [both AEs
19 in one patient]; large intestinal obstruction and vomiting [both AEs in one patient]). There
20 were seven deaths altogether; all were related to the disease under investigation. Three
21 of these deaths had an intercurrent serious AE ($n=1$ patient each: pneumocystis carinii
22 pneumonia; intra-abdominal haemorrhage; small intestinal obstruction). The AE of
23 pneumocystis carinii pneumonia was thought to be secondary to bone pancytopenia and
24 was considered by the investigator as related to olaparib.
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38 When considering all patients who received 300 or 400 mg BD TAB (during dose-
39 escalation and randomized expansion phases), 7/24 (29% [22% in randomized
40 expansion phase]) and 14/23 (61% [65% in randomized expansion phase]) patients
41 required ≥ 1 dose reduction because of AEs (mainly due to gastrointestinal toxicities,
42 fatigue, anaemia), respectively. Six patients who started at 400 mg TAB BD required ≥ 2
43 dose de-escalations; dose reductions were more common during the first two cycles of
44 therapy compared with other doses and CAP. Online Resource 1, Supplementary Table
45 7 summarizes drug interruptions and dose reductions for groups 6 and 8. Median time
46 on treatment for ovarian cancer patients receiving 400 mg TAB BD was 212 days,
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1 although the median duration for patients receiving the cohort starting dose of 400 mg
2 TAB BD before requiring a dose modification was only 51 days.

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5 Intermittent dosing (group 8) did not affect patient adherence to treatment; mean
6 compliance was 94.6–97.4% across schedules. For the alternative-scheduling cohorts
7 (group 8), the inclusion criteria were amended to restrict enrolment for patients with
8 higher baseline haemoglobin (Online Resource 1, Supplementary Table 1), resulting in a
9 lower incidence of anaemia overall (12 cases, 19.4%) relative to the patients in the
10 previous expansion cohorts (groups 1 and 6; 22/64, 34.4%). Three and two cases of G3
11 anaemia were observed in the intermittent and continuous-dosing groups (3/31, 9.6%;
12 2/31, 6.4%; Table 4), respectively.

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15 The most common AEs observed in group 8 were nausea and vomiting (reported in 82%
16 and 68% of patients, respectively; Table 4). Intermittent administration of 400 mg BD led
17 to G3 vomiting in 18.8% of cases (3/16 patients), while only one case was reported in
18 each of the other dose schedules (6–7%). Moreover, the 400 mg BD intermittent dose
19 level had the most patients requiring dose reductions (6/16, 37.5%) because of AEs,
20 compared with 6.7–18.8% of patients in the other dose schedules.

21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 **3.4 Antitumour activity in *gBRCAm* carriers and serous ovarian carcinoma**

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43 The radiological ORR in *gBRCAm* carriers with serous ovarian carcinoma from groups 1
44 and 6 ($n=53$ total: 200 mg BD TAB, $n=8$; 300 mg BD TAB, $n=13$; 400 mg BD TAB, $n=12$;
45 400 mg BD CAP, $n=20$) was 30% (16/53; 95% CI 18.3–44.3) across cohorts, although it
46 appeared higher for patients receiving 300 mg TAB BD (5/13, 38%; 95% CI 13.9–68.4)
47 and 400 mg TAB BD (5/12, 42%; 95% CI 15.2–72.3). The RR based on a RECIST
48 response and/or CA-125 was 40% (21/53, 95% CI 26.5–54.0).
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1 Analysis of the percentage change in tumour size after 8 and 16 weeks of treatment
2 showed similar efficacy for both 300 and 400 mg TAB compared with 400 mg BD CAP.
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4 The one-sided upper limit of the 80% CI was below the pre-specified criteria of 20%
5 compared with the original formulation (400 mg BD CAP) for both groups at 300 mg BD
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7 TAB (LSmean change in tumour size at week 8: 1.8%, one-sided 80% UCL 12.1) and
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9 400 mg BD TAB (LSmean change in tumour size at week 8: -10.5%, one-sided 80%
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11 UCL 0), indicating similar efficacy. However, the 200 mg BD CAP dose failed to meet the
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13 criteria to be considered similar to 400 mg BD CAP (difference in LSmeans at week 8:
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15 8.6%, one-sided 80% UCL 21.1). Consistent results were obtained after 16 weeks of
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17 therapy (Tables 5 and 6, Online Resource 1, Supplementary Figure 2). For patients in
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19 the alternative-scheduling cohorts (group 8), only 200 mg TID continuous and 400 mg
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21 BD intermittent dose schedules were considered non-inferior to 400 mg BD CAP (Table
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23 6, Online Resource 1, Supplementary Figure 2).
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4 DISCUSSION

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3 This adaptive trial was planned as a comparative bioavailability study to select the
4 optimal dose of a TAB olaparib formulation so as to simplify drug administration. Prior
5 clinical trials using the CAP olaparib formulation reported a direct association between
6 dose and antitumour activity in gBRCAm carriers [8-10]. We conducted a comparison of
7 olaparib TAB bioavailability, efficacy, and safety with those of 400 mg CAP BD and
8 identified 300 mg TAB BD as the recommended TAB monotherapy dose for investigation
9 in olaparib Phase III clinical trials.
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12 PK modelling predicted that a 200 mg BD TAB dose would deliver multiple-dose
13 exposure within the range of exposures observed with 400 mg BD CAP [7]. However,
14 direct intra-subject comparison of steady-state exposure for the six patients treated at
15 200 mg BD TAB showed that, although the gmean $C_{max,ss}$ achieved was similar to 400
16 mg BD CAP, gmean AUC_{ss} and $C_{min,ss}$ were approximately 20% and 50% lower,
17 respectively. Consequently, stage 2 of the study was pursued to assess tolerability and
18 antitumour activity of higher TAB doses.
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21 The dose-escalation phase established 400 mg BD TAB as the MTD based on
22 haematological toxicities at 450 mg BD. However, as patient numbers in this phase were
23 small, a randomized comparison between 300 mg BD TAB (lowest dose achieving
24 similar drug exposure to the CAP recommended dose), 400 mg BD TAB (the defined
25 TAB MTD) and the original 400 mg CAP regimen was performed to better determine the
26 tolerability profiles. For patients who were receiving 400 mg BD TAB in the randomized
27 dose-expansion phase, the number of anaemia and gastrointestinal AEs, as well as the
28 number of patients requiring dose reductions, confirmed that olaparib 400 mg BD TAB
29 was not optimally tolerated in this population of heavily pre-treated breast and ovarian
30 cancer patients.
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1 Although antitumour activity was not a primary objective of this study and there were
2 limited numbers of patients in each dose subgroup, it is noteworthy that this is one of the
3 largest series of *gBRCAm* carriers receiving a single-agent PARP inhibitor. The overall
4 response rate across the different cohorts was 30% in *gBRCAm* ovarian cancer patients;
5 these data further support the confirmed anticancer activity of olaparib in patients with a
6 *gBRCAm* [11, 17]. For ovarian cancer patients, the analysis of preliminary data on
7 antitumour activity showed that 300 mg BD TAB was similar to the approved dose of 400
8 mg BD CAP.
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19 We also evaluated olaparib administered in different schedules based on the hypothesis
20 that different patterns of drug exposure may help alleviate common AEs of anaemia,
21 nausea or vomiting. Intermittent PARP inhibition has been investigated in several
22 combinatory trials, mainly with cytotoxic chemotherapy [24-26], but this is, to our
23 knowledge, the first series of patients prospectively enrolled to receive a single-agent
24 PARP inhibitor in different intermittent schedules. In these cohorts, intermittent
25 scheduling did not improve gastrointestinal tolerability; indeed, nausea, vomiting or
26 diarrhoea seemed to be better controlled by reducing the daily amount of drug
27 administered. However, this cohort was conducted only in patients with advanced
28 ovarian carcinoma, where serosal bowel involvement is a common cause of
29 gastrointestinal symptoms, and may not be generalizable to other tumour types.
30 Additionally, preclinical data have indicated that continuous inhibition of PARP is
31 required for maximum efficacy (unpublished data), further supporting continuous rather
32 than intermittent dosing for olaparib monotherapy. Administration of the 600 mg total
33 daily dose as a TID schedule (200 mg TID), while showing similar efficacy, was not
34 considered to improve tolerability over 300 mg BD, with additional patient inconvenience
35 of TID dosing.
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5 CONCLUSION

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3 In conclusion, this multistage clinical trial showed that patients' exposure following tablet
4 doses ≥ 300 mg BD matched or exceeded that of the approved 400 mg BD CAP (8x50
5 mg capsules BD). A dose of 300 mg BD TAB was better tolerated than higher doses,
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8 with similar clinical activity in terms of tumour shrinkage. None of the intermittent-dosing
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10 schedules explored improved both efficacy and tolerability relative to 300 mg BD
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12 continuous dosing. Therefore, continuous dosing of olaparib tablets 300 mg BD (2x150
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14 mg tablets BD) is recommended for olaparib Phase III clinical trials, simplifying drug
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16 administration from 16 capsules to four tablets per day.
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6 COMPLIANCE WITH ETHICAL STANDARDS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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6.2 Disclosure of potential conflicts of interest

JM, VM, AG, CS and KL have no conflicts. SBK has attended Advisory Boards for AstraZeneca and has assisted AstraZeneca with the EMA regulatory submission for olaparib. ED received commercial funding from AstraZeneca to The Christie NHS Foundation Trust for the conduct of this study. MM reports grants from Cancer Research UK during the conduct of this study; grants from Roche, AstraZeneca, GSK; personal fees from Amgen, Roche, GlaxoSmithKline, Eisai, Bristol-Myers Squibb; study fees from Novartis, Astellas (was OSI), Millenium, Abbott (now AbbVie), Clovis Oncology, Pfizer, Bristol-Myers Squibb, Vertex, Eisai, Merck, Immunocore; Advisory Board attendance from Bristol-Myers Squibb; and travel funding from Merck and Immunocore. MF has received provision of drugs for investigator-initiated trials and Advisory Board attendance from AstraZeneca. CG has received personal and non-personal fees from AstraZeneca for Advisory Board attendance, lectures and research funding. RP has received clinical trial funding and Advisory Board payment from AstraZeneca. GR has received funding for Advisory Board attendance from AstraZeneca. SN has received funding for Advisory

1 Board attendance from AstraZeneca and Roche. JL has received personal and non-
2 personal fees from AstraZeneca for Advisory Board attendance and lectures. HS was
3
4 previously employed by AstraZeneca and owns stock in AstraZeneca. AF is employed
5
6 by and owns stock in AstraZeneca. WB is a contract researcher for AstraZeneca. RM
7
8 reports commercial funding for the conduct of this study from AstraZeneca to The Royal
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10 Marsden/Institute of Cancer Research.
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FIGURE LEGENDS

Fig 1 Mean olaparib plasma concentration profile for (a) single oral dosing of the CAP formulation at doses of 50, 100 and 400 mg to patients with advanced solid tumours, (b) following single oral dosing of the TAB formulation at doses of 25, 50 and 250 mg to patients with advanced solid tumours, and (c) following multiple dosing of the TAB (200 mg BD) and CAP (400 mg BD) to patients in group