Table 1

Table 1. Patient demographics and baseline characteristics

	Stage 1						Stage 2											
	Bioavailability assessment/CSP			Dose expansion			Dose expansion, dose-escalation					Dose expansion, randomized TAB/CAP comparison			Dose expansion, randomized TAB alternative dosing schedules			
	Cohort 1	Cohort 2	Cohort 3	Group 1		Group 2	Group 3	Group 4	Group 5	Group 5.1	Group 5.2	Group 6			Group 8			
	Single dose: 50 mg CAP, 25 mg TAB CSP: 400 mg BD CAP	Single dose: 100 mg CAP, 50 mg TAB CSP: 400 mg BD CAP	Single dose: 400 mg CAP, 250 mg TAB CSP: 400 mg BD CAP	200 mg BD TAB	400 mg BD CAP	200 mg TAB and 400 mg CAP – crossover[a]	250 mg BD TAB	300 mg BD TAB	350 mg BD TAB	400 mg BD TAB	450 mg BD TAB	300 mg BD TAB	400 mg BD TAB	400 mg BD CAP	200 mg TID TAB cont	250 mg TID TAB inter (2 weeks on, 1 week off)	400 mg BD TAB inter (1 week on, 1 week off)	400 mg OD TAB cont
Patients enrolled, *n*	6	6	6	13	11	9	6	6	6	7	6	66			16	15	16	15
Patients treated, *n*	6	6	6	13	11	9	6	6	6	6	6	18	17	18	16	15	16	15
Age (years), mean (SD)	61.2 (9.2)	57 (11.4)	53.8 (12.5)	51.9 (8.8)	50.9 (9.8)	58.3 (10.5)	53.2 (17)	56 (10)	49.3 (5.1)	53.4 (8.9)	57.5 (7.9)	55.8 (10.4)	54.2 (11)	52.5 (10.6)	55.6 (10.4)	53.1 (9.2)	54.5 (9.8)	54.5 (10.4)
Sex, *n* (%)																		
Female	4 (67)	2 (33)	3 (50)	13 (100)	10 (91)	8 (89)	6 (100)	5 (83)	6 (100)	5 (71)	6 (100)	18 (100)	17 (100)	18 (100)	16 (100)	15 (100)	16 (100)	15 (100)
Male	2 (33)	4 (67)	3 (50)	0	1 (9)	1 (11)	0	1 (17)	0	2 (29)	0	0	0	0	0	0	0	0
ECOG performance status, *n* (%)																		
0	3 (50)	5 (83)	4 (67)	8 (61)	5 (45)	4 (44)	5 (83)	4 (67)	4 (67)	3 (43)	5 (83)	9 (50)	3 (18)	11 (61)	11 (69)	7 (47)	9 (56)	11 (73)
1	3 (50)	1 (17)	2 (33)	4 (31)	6 (55)	5 (56)	1 (17)	1 (17)	2 (33)	3 (43)	1 (17)	7 (39)	12 (70)	7 (39)	5 (31)	8 (53)	7 (44)	4 (27)
2	0	0	0	1 (8)	0	0	0	1 (17)	0	1 (14)	0	2 (11)	2 (12)	0	0	0	0	0
Primary tumour location, *n* (%)																		

Ovarian[b]	1 (17)	2 (33)	2 (33)	9 (69)[e]	7 (64)	2 (22)	3 (50)	1 (17)	4 (67)	2 (29)	4 (67)	13 (72)	12 (71)	13 (72)	16 (100)	15 (100)	16 (100)	15 (100)
Breast	0	0	1 (17)	4 (31)	4 (36)	3 (33)	2 (33)	3 (50)	2 (33)	3 (43)	2 (33)	5 (28)	5 (29)	5 (28)	0	0	0	0
Colorectal	3 (50)	1 (17)	0	0	0	3 (33)	0	0	0	0	0	0	0	0	0	0	0	0
Pancreas	0	0	0	0	0	1 (11)	0	0	0	0	0	0	0	0	0	0	0	0
Lung	1 (17)	1 (17)	1 (17)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Prostate	0	1 (17)	0	0	0	0	0	1 (17)	0	0	0	0	0	0	0	0	0	0
Other	1 (17)	1 (17)	2 (33)	0	0	0	1 (17)	1 (17)	0	2 (29)	0	0	0	0	0	0	0	0
Prior chemotherapy regimes, *n* (%)																		
0	0	2 (33)	1 (17)	0	0	0	0	1 (17)	0	1 (14)	0	0	0	1 (6)	0	0	0	0
1	2 (33)	1 (17)	2 (33)	0	2 (18)	0	1 (17)	0	0	1 (14)	2 (33)	1 (6)	2 (12)	3 (17)	2 (13)	1 (7)	1 (6)	2 (13)
2	0	2 (33)	0	2 (15)	3 (27)	3 (33)	2 (33)	1 (17)	2 (33)	3 (43)	0	2 (11)	1 (6)	4 (22)	2 (13)	1 (7)	2 (13.5)	5 (33)
3	0	0	2 (33)	2 (15)	3 (27)	1 (11)	2 (33)	1 (17)	0	1 (14)	2 (33)	3 (17)	8 (47)	3 (17)	5 (31)	6 (40)	3 (19)	4 (27)
4	0	0	0	2 (15)	0	2 (22)	0	0	3 (50)	1 (14)	0	5 (28)	1 (6)	5 (28)	5 (31)	3 (20)	5 (31)	2 (13)
≥5	4 (67)	1 (17)	1 (17)	7 (54)	3 (27)	3 (33)	1 (17)	3 (50)	1 (17)	0	2 (33)	7 (39)	3 (18)	2 (11)	2 (13)	4 (27)	5 (31)	2 (13)
Median	5	2	2	6	3	4	3	4	4	2	3	4	3	3	3	3	4	3
BRCA mutation status, *n* (%)																		
*BRCA1/2*m	NC	NC	NC	13 (100)	10 (91)	NC	NC	NC	NC	NC	NC	18 (100)	17 (100)	18 (100)	16 (100)	15 (100)	16 (100)	15 (100)
Negative				0	0							0	0	0	0	0	0	0
Unknown				0	1 (9)							0	0	0	0	0	0	0
Baseline haemoglobin CTCAE grade,[c] *n* (%)	CSP (400 mg BD CAP)																	
0	9 (53)			7 (58)	9 (82)	4 (57)	5 (83)	3 (50)	4 (67)	3 (50)	3 (50)	6 (33)	8 (47)	12 (67)	11 (69)	11 (73)	13 (81)	10 (67)
1	8 (47)			5 (42)	2 (18)	3 (43)	1 (17)	3 (50)	2 (33)	3 (50)	3 (50)	10 (56)	6 (35)	6 (33)	5 (31)	4 (27)	3 (19)	5 (33)
2	0			0	0	0	0	0	0	0	0	2 (11)	3 (18)	0	0	0	0	0

Patient demographic and baseline characteristic for ovarian cancer patients included in efficacy analyses											
Ovarian cancer patients only		8 (62)[e]	7 (64)		13 (72)	12 (71)	13 (72)	16 (100)	15 (100)	16 (100)	15 (100)
Platinum-sensitivity,[d] *n* (%)											
Sensitive		NC	NC		3 (23)	6 (50)	7 (54)	6 (38)	4 (27)	5 (31)	9 (60)
Resistant					7 (54)	5 (42)	6 (46)	10 (63)	11 (73)	11 (69)	6 (40)
No prior plat					1 (8)	0	0	0	0	0	0
Unknown					2 (15)	1 (8)	0	0	0	0	0
BRCA mutation status, *n* (%)											
*BRCA1/2*m		8 (100)	7 (100)		13 (100)	12 (100)	13 (100)	16 (100)	15 (100)	16 (100)	15 (100)
Negative		0	0		0	0	0	0	0	0	0
Unknown		0	0		0	0	0	0	0	0	0

(%), percentage of patients treated with olaparib; NC, data not collected; PKP, pharmacokinetic phase

[a]Used to directly compare steady-state CAP and TAB PK; [b]Includes patients with primary peritoneal or fallopian tube tumour; [c]Patients with a baseline value and at least one on-treatment value; percentages have been calculated using the number of patients at baseline; [d]Assessed by the investigator; [e]One patient was mis-stratified as having a primary tumour location of breast cancer, when this should have been stratified as ovarian cancer. This patient was excluded from the ovarian cancer subset as this was based on randomisation stratification data but included as ovarian cancer in summaries of primary tumour location

Table 2. Steady-state PK parameters (day 29) for olaparib following multiple dosing with TAB and CAP during the efficacy expansion phase of groups 1 and 6

	Olaparib CAP and TAB dose during the dose-expansion phase				
	Dose expansion 1 (group 1)		Dose expansion 2 (group 6)		
	200 mg BD TAB	**400 mg BD CAP**	**300 mg BD TAB**	**400 mg BD TAB**	**400 mg BD CAP**
Day 29[a]	(*n* = 11)	(*n* = 10)	(*n* = 17)	(*n* = 10)	(*n* = 17)
$C_{max,ss}$, µg/mL	6.88 (4.01–10.4)	5.70 (2.38–10.9)	9.37 (2.28–14.7)	12.0 (8.45–16.9)	6.36 (3.88–13.3)
$C_{min,ss}$, µg/mL	1.00 (0.28–3.10)	1.86 (0.53–6.67)	1.84 (0.34–3.83)	2.01 (0.76–3.61)	1.04 (0.23–8.49)
$AUC_{0-12,SS}$, µg·h/mL	36.1 (16.0–69.0)	43.1 (18.1–98.6)	58.4 (23.1–96.0)	72.8 (44.8–106)	41.5 (18.7–147)

[a]Only subjects remaining on the starting dose at day 29 were included in the summary statistics. All data expressed as gmean (range)

Table 3

Table 3. Summary of actual treatment exposure and AEs of grade ≥3 (occurring in more than one patient) in the dose-expansion phase for groups 1 (200 mg TAB and 400 mg CAP) and 6 and dose-escalation groups 3, 4, 5, 5.1 and 5.2

	Group 1		Group 3	Group 4	Group 5	Group 5.1	Group 5.2		Group 6	
	200 mg BD TAB *n* = 13	400 mg BD CAP *n*=11	250 mg BD TAB *n* = 6	300 mg BD TAB *n* = 6	350 mg BD TAB *n* = 6	400 mg BD TAB *n* = 6	450 mg BD TAB *n* = 6	300 mg BD TAB *n* = 18	400 mg BD TAB *n* = 17	400 mg BD CAP *n* = 18
Actual olaparib treatment exposure, days, median (range)	114 (0–844)	193 (34–416)	249.5 (22–551)	326.5 (50–491)	115.5 (8–380)	110.5 (44–196)	207 (57–240)	135 (53–281)	166 (17–281)	178 (62–277)
Any Grade ≥3 AE, *n* (%)	5 (39)	2 (18)	1 (17)	4 (67)	2 (33)	5 (83)	4 (67)	11 (61)	10 (59)	7 (39)
Blood and lymphatic system disorders										
Anaemia	0	0	0	2 (33)	1 (17)	1 (17)	3 (50)	4 (22)	5 (30)	4 (22)
Neutropenia	0	0	0	0	0	1 (17)	1 (17)	2 (11)	0	1 (6)
Thrombocytopenia	0	0	0	0	0	0	1 (17)	0	3 (18)	0
Gastrointestinal disorders										
Abdominal pain	1 (8)	0	0	0	0	1 (17)	0	2 (11)	0	0
Diarrhoea	0	1 (9)	0	0	0	0	0	2 (11)	0	0
Nausea	1 (8)	1 (9)	0	0	0	0	0	0	2 (12)	0
Vomiting	1 (8)	1 (9)	0	0	0	0	0	0	0	1 (6)
General disorders										
Oedema peripheral	0	1 (9)	0	0	0	0	0	0	0	0
Fatigue	5 (39)	1 (9)	0	0	0	2 (33)	0	3 (17)	2 (12)	0

Non-cardiac chest pain	1 (8)	0	0	0	0	0	0	0	0	0
Metabolism and nutritional disorders										
Decreased appetite	1 (8)	0	0	0	0	0	0	0	0	0
Musculoskeletal disorders										
Back pain	1 (8)	0	0	0	0	0	0	0	0	0
Musculoskeletal pain	0	0	0	0	0	0	0	0	1 (6)	0
Respiratory, thoracic and mediastinal disorders										
Dyspnoea	1 (8)	1 (9)	0	0	0	0	1 (17)	0	1 (6)	0

Table 4 Click here to download Table Table 4.docx

Table 4. Summary of actual treatment exposure and number (%) of patients who had at least one AE of any grade (occurring in more than three patients in any treatment group) and AEs of grade ≥3 (occurring in more than one patient) in group 8 (expansion phase, alternative dosing schedules)

	Olaparib randomized tablet formulation for group 8			
	200 mg TID TAB cont	**250 mg TID TAB inter (2 weeks on, 1 week off)**	**400 mg BD TAB inter (1 week on, 1 week off)**	**400 mg OD TAB cont**
	***n*=16**	***n*=15**	***n*=16**	***n*=15**
Actual olaparib treatment exposure, median (range)	164 (4–390)	221 (5–413)	271 (58–366)	211 (26–463)

AE, *n* (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Any AE	15 (94)	6 (38)	15 (100)	7 (47)	16 (100)	6 (38)	14 (93)	5 (33)
Blood and lymphatic system disorders								
Anaemia	3 (19)	1 (6)	5 (33)	3 (20)	1 (6)	0	3 (20)	1 (7)
Thrombocytopenia	0	0	2 (13)	2 (13)	0	0	0	0
Gastrointestinal disorders								

Abdominal pain	3 (19)	0	4 (27)	1 (7)	6 (38)	1 (6)	3 (20)	2 (13)
Constipation	2 (13)	0	6 (40)	0	6 (38)	0	7 (47)	0
Diarrhoea	2 (13)	1 (6)	2 (13)	0	9 (56)	1 (6)	3 (20)	0
Nausea	13 (81)	0	12 (80)	1 (7)	13 (81)	2 (13)	10 (67)	0
Small intestinal obstruction	0	0	1 (7)	0	0	0	2 (13)	2 (13)
Vomiting	8 (50)	1 (6)	10 (67)	1 (7)	12 (75)	3 (19)	6 (40)	1 (7)
General disorders								
Fatigue	8 (50)	2 (13)	8 (53)	0	10 (63)	1 (6)	10 (67)	0
Gamma-glutamyltransferase increased	0	0	0	0	0	0	2 (13)	2 (13)
Infections								
Urinary tract infection	0	0	0	0	2 (13)	0	4 (27)	0
Metabolism and nutritional disorders								
Decreased appetite	4 (25)	1 (6)	6 (40)	0	5 (31)	0	5 (33)	0

Musculoskeletal disorders								
Arthralgia	2 (13)	0	0	0	4 (25)	0	3 (20)	0
Nervous system disorders								
Dysgeusia	5 (31)	0	2 (13)	0	4 (25)	0	0	0
Respiratory, thoracic and mediastinal disorders								
Cough	1 (6)	0	1 (7)	0	3 (19)	0	4 (27)	0
Dyspnoea	0	0	2 (13)	0	4 (25)	0	1 (7)	0

Table 5. Analysis of percentage change in tumour size at week 8 and week 16 – dose-expansion group 1 and group 6 – patients with ovarian cancer

	Group 1		Group 6		
	200 mg BD TAB (n=8)	**400 mg BD CAP (n=7)**	**300 mg BD TAB (n=13)**	**400 mg BD CAP (n=13)**	**400 mg BD TAB (n=12)**
Week 8					
Unadjusted mean	–3.7%	–12.4%	–16.8%	–17.0%	–28.7%
LS mean[a]	–3.7%	–12.4%	–16.1%	–17.9%	–28.4%
Treatment effect[a]					
Difference in LS means	8.6%		1.8%		–10.5%
80% CI	–10.7, 28.0		–14.0, 17.6		–26.6, 5.6
95% CI	–22.5, 39.8		–22.8, 26.4		–35.5, 14.6
Two-sided *P* value	0.557		0.881		0.401
One-sided 80% UCL	21.1		12.1		0.0
Week 16					

Unadjusted mean	2.0%	–15.3%	–11.5%	–16.3%	–26.6%
LS mean[a]	1.9%	–15.2%	–10.6%	–17.6%	–26.2%
Treatment effect[a]					
Difference in LS means	17.1%		7.0%		–8.6%
80% CI	–9.8, 44.1		–16.1, 30.0		–32.1, 14.9
95% CI	–26.2, 60.5		–28.9, 42.8		–45.1, 28.0
Two-sided *P* value	0.406		0.696		0.637
One-sided 80% UCL	34.5		22.0		6.8

CI, confidence interval; LS, least squares; UCL, upper confidence limit. [a]Adjusted for baseline tumour size

Table 6. Analysis of percentage change in tumour size at week 8 and week 16 – randomized dose-expansion groups 1 and 6, and group 8 – patients with ovarian cancer

	Group 1 and 6	Group 8			
	400 mg BD CAP cont (n=20)	**200 mg TID TAB cont (n=15)**	**250 mg TID TAB inter (2 weeks on, 1 week off) (n=14)**	**400 mg BD TAB inter (1 week on, 1 week off) (n=16)**	**400 mg OD TAB cont (n=15)**
Week 8					
Unadjusted mean	–15.4%	–17.8%	–5.1%	–15.8%	–9.0%
LS mean	–19.35%	–16.4%	–5.4%	–14.8%	–3.4%
Treatment effect versus 400 mg BD CAP[a]					
Difference in LS means		2.91%	13.9%	4.6%	15.9%
80% CI		–9.1, 14.9	1.2, 26.7	–7.6, 16.8	3.6, 28.3
95% CI		–15.6, 21.4	–5.7, 33.6	–14.1, 23.4	–3.1, 34.9
Two-sided *P* value		0.756	0.162	0.627	0.099

One-sided 80% UCL		10.8	22.3	12.6	24.0
Week 16					
Unadjusted mean	–15.9%	–12.8%	–7.2%	–14.4%	–11.3%
LS mean	–19.7%	–10.6%	–9.1%	–14.3%	–3.3%
Treatment effect versus 400 mg BD CAP[a]					
Difference in LS means		9.1%	10.6%	5.4%	16.4%
80% CI		–8.5, 26.7	–8.0, 29.2	–12.5, 23.2	–1.7, 34.4
95% CI		–18.0, 36.2	–18.1, 39.3	–22.1, 32.8	–11.4, 44.1
Two-sided *P* value		0.507	0.465	0.699	0.245
One-sided 80% UCL		20.6	22.8	17.0	28.2

[a]Data from the 400 mg BD capsule arm from ovarian cancer patients in groups 1 and 6 have been combined to use as a comparator in analyses.

Analysis for group 8 was performed using an analysis of covariance with factors for treatment group, baseline sum of target lesions, prior platinum chemotherapy status, number of prior chemotherapy regimens and whether there was peritoneal involvement at baseline

Figure 1

Figure 1

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