Clinical Study Report Synopsis

Drug Substance	Olaparib
Study Code	D081BC00001
Edition Number	1

A Phase I, Open-label Study to Assess the Safety and Tolerability of Doses of Olaparib Tablet in Japanese Patients with Advanced Solid Malignancies

Study dates:	First patient enrolled: 25 March 2013 Last patient enrolled: 31 October 2013
Phase of development:	Clinical pharmacology (I)

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

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Objectives and outcome variables are presented in Table S1.

Table S1 Objectives and outcome variables

Objective Priority	Type	Description	Outcome Variable Description
Primary	Safety	To investigate the safety and tolerability of olaparib tablet when given oral to Japanese patients with advanced solid malignancies.	AEs Vital signs: Blood pressure, pulse, SPO2, and body temperature Physical examination including ECOG performance status Pulmonary function safety assessments ECG Laboratory safety assessment Duration of exposure Dose intensity
Secondary	PK	To characterise the PK profile of olaparib following single oral dosing and at steady state after twice-daily dosing of oral tablet formulation of olaparib.	For the single dose part of the study: Cmax, tmax, λz, t½λz, AUC(0-12), AUC(0-t), AUC, CL/F, Vz/F, and MRT. For the multiple dose part of the study: Css, max, tss, max, Css, min, AUCss, Rac(Cmax), Rac(AUC), and TCP
Secondary	Safety	To define the MTD if possible. However, the dose was not escalated beyond that previously shown to be the MTD in a Western population.	Number of patients with DLT

Table S1 Objectives and outcome variables

Objective Priority	Type	Description	Outcome Variable Description
Exploratory	Efficacy	To obtain a preliminary assessment of the anti-tumour activity of olaparib by evaluation of tumour response using RECIST Version 1.1.	ORR, best objective response, and percentage change in tumour size at each visit for patients in tumour response analysis set.
Exploratory	Pharmacodynamic[a]	To obtain a preliminary assessment of the visualised drug distribution in tumour tissue of olaparib to performed molecular image analysis by the MALDI-imaging mass spectrometry system.	Not applicable.

[a] Results for this exploratory research will be reported separately from the CSR for the main study.
AE Adverse event; AUC Area under plasma concentration-time curve; $AUC_{(0-12)}$ Area under plasma concentration-time curve from 0 to 12 hour; $AUC_{(0-t)}$ Area under plasma concentration-time curve from 0 to time t; AUC_{ss} Area under the plasma concentration-time curve at steady state; CL/F Oral clearance of drug from plasma; C_{max} Maximum plasma concentration; $C_{ss, max}$ Maximum (peak) steady state drug concentration in plasma during dosing interval; $C_{ss, min}$ Minimum (trough) steady state drug concentration in plasma during dosing interval; CSR Clinical Study Report; DLT Dose-limiting toxicity; ECG Electrocardiogram; MRT Mean residence time; MTD Maximum tolerated dose; PK Pharmacokinetic; $R_{ac(AUC)}$ Accumulation ratios in terms of area under plasma concentration-time curve; $R_{ac(Cmax)}$ Accumulation ratios in terms of maximum plasma concentration; RECIST Response Evaluation Criteria in Solid Tumours; $t_{½\lambda z}$ Terminal half-life, TCP Temporal change parameter; t_{max} Time to reach maximum plasma concentration; $t_{ss, max}$ time of maximum concentration at steady state; V_z/F Oral volume of distribution (apparent) during terminal rate constant phase; λ_z terminal rate constant.

Study design

This was a Phase I, open-label, multi-centre study of olaparib tablet administered orally in Japanese patients with advanced solid malignancies.

The study design allowed an escalation of dose with intensive monitoring to ensure safety of the patients. In Cohort 1, at least 3 patients and up to 6 evaluable patients were to be enrolled. If the dose in this cohort was considered to be tolerated by the Safety Review Committee (SRC), then it was to be escalated to the next cohort. In the next cohort, 6 patients were planned to be enrolled to confirm safety and tolerability. If 2 or more patients of the evaluable 6 patients experienced dose-limiting toxicity (DLT) in the next cohort, then that dose was considered not tolerated. Six patients were to be enrolled in Cohort 1 to assess if that dose was tolerable or an intermediate dose between previous cohort and this cohort could be explored to identify a maximum tolerated dose (MTD) dose.

In this study, the dose for Cohort 1 patients was 200 mg bid and for Cohort 2 patients was 300 mg bid. Therefore, 200 mg bid group is referred to as Cohort 1 and the 300 mg bid group is referred to as Cohort 2 in this document.

If 300 mg bid dose in Cohort 2 was concluded as tolerated by the SRC, then 12 patients were to be enrolled in the expansion part of the study.

Target subject population and sample size

The target population included Japanese patient with advanced solid malignancy, aged ≥20 years with Eastern Co-operative Oncology Group (ECOG) performance status 0 to 1.

The number of patients was based on the desire to obtain adequate tolerability, safety, and pharmacokinetic (PK) data while exposing as few patients as possible to the study treatment and procedures. Approximately 18 patients were planned to be enrolled in this study. The number of patients required in the expansion part was 12, considering the number of patients in the dose escalation part.

Investigational product and comparators: Dosage, mode of administration, and batch numbers

Olaparib 200 mg (batch no. 6739.19) and 100 mg (batch no. 6739.16) tablets manufactured by AstraZeneca, were used in this study. Cohort 1 received 200 mg bid, Cohort 2 and Cohort 3 received 300 mg bid, orally.

Duration of treatment

For each cohort, single dose was administered on Day 1, followed by a washout period of 1 day. The single dose was followed by multiple dosing, each cycle comprising of 28 days. The patients continued to receive olaparib as long as they continued to show clinical benefit.

Statistical methods

Safety and tolerability were assessed in terms of adverse events (AEs), vital signs, physical examination including Eastern Co-operative Oncology Group performance status, pulmonary function safety assessments, electrocardiogram (ECG), laboratory safety assessment, duration of exposure, and dose intensity. These safety measures were listed and summarised descriptively using the safety analysis set. Data from all cycles of initial treatment were combined in the presentation of safety data.

Pharmacokinetic sampling was performed only during the dose escalation part of the study Plasma concentrations of olaparib were summarised by nominal sample time. In the dose escalation part, plasma concentrations and derived PK parameters were summarised by dose level. Parameters following single and multiple dosing were summarised separately.

Tumour response (according to RECIST 1.1) data were summarised for patients included in the tumour response analysis set and patients excluded from the tumour response analysis set separately. Tumour response data were listed and summarised by dose level, according to the best objective response categories: Complete response (CR), partial response (PR), stable disease ≥8 weeks, progressive disease (PD), and not evaluable. The absolute value and percentage change in target lesion tumour size from baseline at each visit were summarised

using descriptive statistics. The 95% exact (Clopper-Pearson) confidence interval (CI) of ORR was produced and presented by dose level.

All patients who received at least 1 dose of olaparib were included in the safety analysis set. Patients who received at least 1 dose of olaparib and for whom an adequate PK profile was obtained were included in the PK analysis set. Patients who received at least 1 dose of olaparib and had a measurable disease at baseline were included in the tumour response analysis set.

Subject population

Table S2 presents a summary of patient disposition.

A total of 28 patients were enrolled in this study from 3 centres in Japan. Twenty three patients (4 patients in Cohort 1, seven patients in Cohort 2, and 12 patients in Cohort 3) received the study treatment. Five patients were not assigned to the study treatment due to the following reason: Did not fulfil the eligibility criteria (2 patients), subject's decision (2 patients), and 1 patient gave priority to the treatment of brain metastasis.

Two patients were ongoing olaparib treatment and 21 patients discontinued the study treatment. The most common reason for discontinuation of the study treatment was worsening of the condition under investigation (18 [78.3%] patients).

Of the 23 patients who received the study treatment, 2 (8.7%) patients were ongoing in the study at the final data cut-off and continued receiving the study treatment and 21 (91.3%) patients were terminated from the study and had discontinued the study treatment. The most common reason for termination from the study was worsening of condition under investigation (17 [73.9%] patients). One patient in Cohort 3 died due to worsening of the condition under investigation.

Overall, the demographic and baseline characteristics were representative of the intended population. The mean age of patients was 54.1 years (range: 34 years to 77 years) with 10 (43.5%) patients in the age group of ≥50 to <65 years. There were 8 (34.8%) male patients and 15 (65.2%) female patients in the study.

Table S2 Patient disposition (All patients)

	Number (%) of Patients			
	Cohort 1 Olaparib 200 mg BID	**Cohort 2 Olaparib 300 mg BID**	**Cohort 3 Olaparib 300 mg BID**	**Total**
Patients enrolled[a]				28
Patients assigned to treatment	4 (100.0)	7 (100.0)	12 (100.0)	23 (100.0)
Patients who were not assigned to treatment				5

Table S2 Patient disposition (All patients)

	Number (%) of Patients			
	Cohort 1 Olaparib 200 mg BID	**Cohort 2 Olaparib 300 mg BID**	**Cohort 3 Olaparib 300 mg BID**	**Total**
Eligibility criteria not fulfilled				2
Subject decision				2
Other				1
Patients who received treatment	4 (100.0)	7 (100.0)	12 (100.0)	23 (100.0)
Patients who did not receive treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients ongoing olaparib at final data cut off[b]	1 (25.0)	0 (0.0)	1 (8.3)	2 (8.7)
Patients who discontinued treatment[b]	3 (75.0)	7 (100.0)	11 (91.7)	21 (91.3)
Subject decision	0 (0.0)	0 (0.0)	1 (8.3)	1 (4.3)
Adverse event	1 (25.0)	1 (14.3)	0 (0.0)	2 (8.7)
Condition under investigation worsened	2 (50.0)	6 (85.7)	10 (83.3)	18 (78.3)
Patients ongoing study at final data cut off	1 (25.0)	0 (0.0)	1 (8.3)	2 (8.7)
Patients who terminated study	3 (75.0)	7 (100.0)	11 (91.7)	21 (91.3)
Subject decision	0 (0.0)	0 (0.0)	1 (8.3)	1 (4.3)
Adverse event	1 (25.0)	1 (14.3)	0 (0.0)	2 (8.7)
Condition under investigation worsened	2 (50.0)	6 (85.7)	9 (75.0)	17 (73.9)
Death	0 (0.0)	0 (0.0)	1 (8.3)	1 (4.3)

[a] Informed consent received.
[b] Percentages were calculated from number of patients assigned to treatment.
bid Twice-daily
Data derived from Table 11.1.1.

Summary of efficacy results

Of the 22 patients with evaluable RECIST data, none of the patients showed response (CR or PR) in any of the cohorts. Of these patients, 1 (25.0%) patient in Cohort 1, two (33.3%) patients in Cohort 2, and 4 (33.3%) patients in Cohort 3 had stable disease response. One (8.3%) patient in Cohort 3 had unconfirmed PR. There were 2 (50.0%) patients in Cohort 1, four (66.7%) patients in Cohort 2, and 8 (66.7%) patients in Cohort 3 who had PD response. One (25.0%) patient in Cohort 1 was not evaluable. No patients in Cohorts 1 and Cohort 2 had any reduction in the target lesion size at Week 8, but 3 patients out of 12 patients in Cohort 3 had slide reduction in the target lesion size.

Given that there was no response in any of the cohorts, the ORR was also 0.0% for Cohort 1 (95% CI= 0.00 to 0.60), Cohort 2 (95% CI= 0.00 to 0.46), and Cohort 3 (95% CI= 0.00 to 0.26).

In total, 9 patients (1 patient in Cohort 1, four patients in Cohort 2, and 4 patients in Cohort 3) had PD based on the RECIST evaluation prior to Week 8. Therefore, for these 9 patients, 20% increase in target lesion size from baseline was imputed at Week 8. As a result, all patients in Cohort 2 had a 20% increase in the target lesion size.

One patient in Cohort 1 had 5.3% increased target lesion size on Day 48 (prior to Week 8) from baseline. For this patient, using a linear regression to the patient's baseline and the assessment on Day 48, an estimated value (6.1% increase) was imputed for the change from baseline at Week 8.

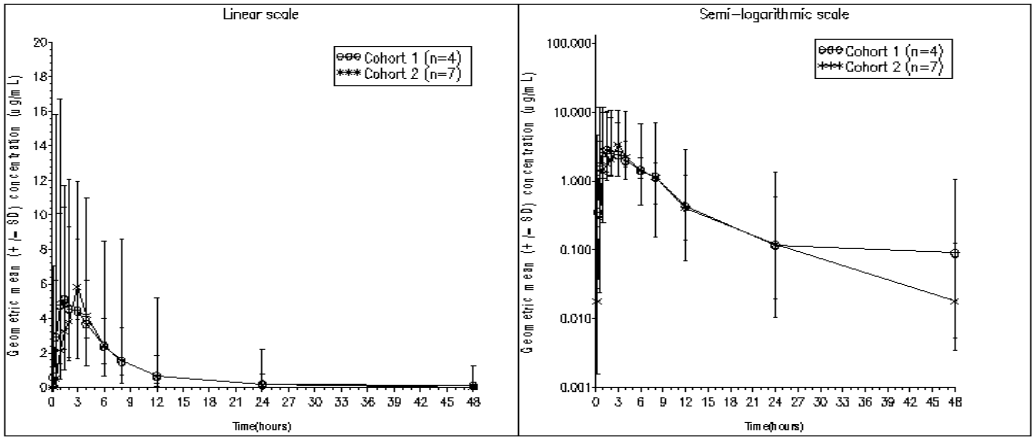
In Cohort 3, 1 patient (E0001006) had >30% reduction in target lesion size on Day 57 and had an unconfirmed PR on first RECIST evaluation. On second RECIST evaluation, this patient had PD (new lesion) after 8 weeks of the first CT. This patient had received previous cancer therapy for ovarian cancer.

Summary of pharmacokinetic results

The geometric mean (Gmean) plasma concentration of olaparib following single dose of olaparib is shown in Figure S1.

Following single oral dose administration of olaparib, absorption of drug in both the dose levels was relatively rapid with median Time to reach peak or maximum concentration (t_{max}) of 2 hours (Cohort 1: 2.00 hours and Cohort 2: 1.98 hours) and an individual patient range of 1.00 hour to 3.00 hours across the 2 dose levels. The plasma concentrations following the peak appeared to decline biphasically and the mean terminal half-life ($t_{½λz}$) was estimated to be 13.24 hours for Cohort 1 and 9.430 hours for Cohort 2 (individual-patient range across the 2 cohorts: 6.45 hours to 18.6 hours).

Figure S1 **Geometric mean (±SD) plasma concentrations (ug/mL) of olaparib (single-dose) (PK analysis set)**



PK Pharmakokinetic; SD Standard deviation.

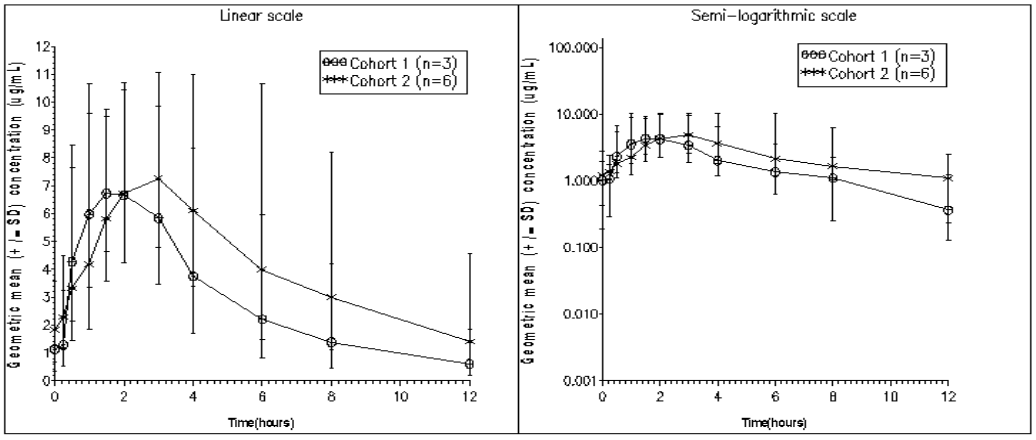
The Geometric mean (Gmean) maximum plasma concentration (C_{max}) in Cohort 1 and Cohort 2 was estimated to be 6.697 µg/mL and 7.743 µg/mL, respectively. The Gmean AUC in Cohort 1 and Cohort 2 was estimated to be 61.97 µg*h/mL and 46.21 µg*h/mL, respectively.

There was observed wide inter-patient variability of plasma concentration and exposure. Especially, 1 patient in Cohort 1 showed considerably higher plasma concentration and exposure compared with other patient of the same cohort. However the reason behind an extremely higher exposure in this patient was not identified.

The Gmean plasma concentration of following multiple dose of olaparib is shown in Figure S2. Since the patient with relatively higher exposures was withdrawn before Day 15 of multiple-dose period due to an AE, the plasma concentrations at steady state were unavailable for this patient. Also the plasma concentration at steady state was not obtained from Patient E0002002 in Cohort 2 as the patient was terminated from the study.

Following bid dose administration of olaparib, absorption of the drug in in both the dose levels was still rapid with median $t_{ss,max}$ of 1.50 hours in Cohort 1 and 3.00 hours in Cohort 2 and an individual patient range of 1.00 hour to 3.93 hours. There was no marked delay of $t_{ss,max}$ after multiple dosing compared with single-dose. The plasma concentration-time profiles were similar for both the cohorts. Due to limited sampling points (namely up to 12 hours), it was not possible to adequately determine $t_{½\lambda z}$ from these profiles.

Figure S2 Geometric mean (±SD) plasma concentrations (ug/mL) of olaparib (multiple-dose) (PK analysis set)



PK Pharmacokinetic; SD Standard deviation.
Data derived from Figure 11.2.2.2.2.1.

The Gmean $C_{ss,max}$ in Cohort 1 and Cohort 2 was estimated to be 7.668 µg/mL and 8.434 µg/mL, respectively. The Gmean AUC_{ss} in Cohort 1 and Cohort 2 was estimated to be 36.50 µg*h/mL and 52.34 µg*h/mL, respectively. Although the dose-normalised exposures showed wide inter-patient variability following both single and multiple dose, they were almost comparable between 2 dose levels with the exception of considerably higher exposure observed after single dose to 1 patient E0001003 in Cohort 1.

The plasma concentration was increased by bid dosing at both the dose levels (mean accumulation ratios of $AUC_{(0-12)}$ were 1.834 to 1.930 with individual range of 1.09 to 2.90 across the dose levels).

Summary of safety results

The median total treatment duration was 72 days in Cohort 1, thirty days in Cohort 2, and 56 days in Cohort 3. The median actual treatment duration was 71 days in Cohort 1, twenty-nine days in Cohort 2, and 56 days in Cohort 3.

There were a total of 23 patients in the safety analysis set, of these, 21 patients experienced at least 1 AE. The most commonly reported AEs were: Nausea (1 [25.0%] patient in Cohort 1, 6 [85.7%] patients in Cohort 2, and 3 [25.0%] patients in Cohort 3), decreased appetite (4 [57.1%] patients in Cohort 2 and 3 [25.0%] patients in Cohort 3), anaemia (4 [57.1%] patients in Cohort 2 and 2 [16.7%] patients in Cohort 3), and constipation (2 [28.6%] patients in Cohort 2 and four [33.3%] patients in Cohort 3). The most common study treatment-related

AEs that occurred in Cohort 2 and Cohort 3 were: Decreased appetite and nausea. Adverse events of common terminology criteria for adverse events (CTCAE) grade ≥3 reported in this study were: Pyelonephritis (1 [25.0%] patient in Cohort 1), anaemia (1 [14.3%] patient in Cohort 2), ileus (1 [25.0%] patient in Cohort 1), decreased neutrophil count (2 [28.6%] patients in Cohort 2 and 1 [8.3%] patient in Cohort 3), decreased white blood cell count (2 [28.6%] patients in Cohort 2 and 1 [8.3%] patient in Cohort 3), and decreased lymphocyte count (1 [14.3%] patient in Cohort 2).

None of the patients experienced a DLT. The SRC determined that 300 mg bid was tolerable. Therefore, an MTD for olaparib could be more than 300 mg bid. There were no AEs leading to olaparib dose reduction. However, 2 patients had dose interruption due to AEs of platelet count decreased and pneumonia.

There was 1 SAE of ileus (CTCAE Grade 3) reported in 1 patient in Cohort 1 but it was not causally-related to the study treatment, and this patient discontinued olaparib due to the SAE. One patient from Cohort 2 experienced AE of neutrophil counts decrease and white blood cell counts decrease which led to discontinuation of olaparib, and these AEs were considered to be causally- related to the study treatment by the investigator. Thus there were 2 patients who discontinued olaparib due to AE.

In Cohort 2 and Cohort 3 there were slightly decreased values in erythrocyte, haemoglobin, neutrocyte and leukocyte, and slight increase of creatinine, but mainly not clinically relevant.

There were no clinically significant abnormalities observed in patients exposed to olaparib regarding vital signs, ECG parameters, and physical findings.