AstraZeneca

Revised Clinical Study Protocol	
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A Phase I, Open Label, Two Part study to Determine the Pharmacokinetics of Olaparib 300 mg bd administered as Monotherapy and Olaparib 100 mg bd as Monotherapy and in Combination with Paclitaxel (100mg bd olaparib Plus weekly 80mg/m^2 paclitaxel), in Chinese Patients with Advanced Solid Tumours

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The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	18 May 2015		
2	05 Nov 2015		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

PROTOCOL SYNOPSIS

A Phase I, Open Label, Two Part study to Determine the Pharmacokinetics of Olaparib 300 mg bd administered as Monotherapy and Olaparib 100 mg bd as Monotherapy and in Combination with Paclitaxel (100mg bd olaparib Plus weekly 80mg/m^2 paclitaxel), in Chinese Patients with Advanced Solid Tumours

Study centre(s) and number of subjects planned

This is an open-label, two part study to determine the pharmacokinetics of olaparib in Chinese patients with advanced solid tumours. Approximately 30 Chinese patients with advanced solid tumour are expected to be recruited from 2 partic ipating sites, with 15 patients entered into each of two treatment cohorts.

Study period		Phase of development
Estimated date of first subject enrolled	Q2, 2015	Phase I
Estimated date of last subject completed (Part A)	Q1, 2016	Phase I
Estimated date of last subject completed (Part B)	Q1, 2017	Phase I

Objectives

Primary Objective

- To characterize the single dose pharmacokinetics of olaparib following a 300mg monotherapy dose and a 100mg monotherapy dose in Chinese patients.
- To characterize the steady state pharmacokinetics of olaparib following 300mg bd monotherapy dose, 100mg bd monotherapy dose and 100mg bd dose of olaparib given in combination with weekly paclitaxel (80 mg/m^2)

Secondary objectives

- To determine the safety and tolerability of olaparib when given as monotherapy (300mg bd) and in combination with paclitaxel (100mg bd olaparib plus 80 mg/m^2) in patients with advanced solid tumours.
- To explore the effect of co-administration of paclitaxel (80 mg/m^2) on steady state exposure to olaparib (100 mg bd).

Study design

This is a phase I, open label, two part study to determine the pharmacokinetics of olaparib 300 mg bd administered as monotherapy and olaparib 100 mg bd as monotherapy and in combination with paclitaxel (100mg bd olaparib plus weekly 80mg/m^2 paclitaxel), in Chinese patients with advanced solid tumours.

Part A will assess the pharmacokinetics of olaparib. Approximately 30 patients will enter into this study, with 15 patients enter into each of two treatment cohorts.

- Cohort 1 will investigate the single and multiple dose pharmacokinetics of olaparib following 300mg bd monotherapy dose(s)

- Cohort 2 will investigate the single and multiple dose pharmacokinetics of olaparib following 100mg bd monotherapy dose(s) and the multiple dose pharmacokinetics in the presence of co-administered paclitaxel (80mg/m^2 weekly on Days 1, 8 and 15 of a single 28-day cycle).

A PRIMA database lock will be made at the end of Part A and a clinical study report (CSR) issued with pharmacokinetic and safety data.

Following completion of the Part A, patients will continue to Part B if they are still considered to be receiving benefit by the treating physician.

Part B will assess the safety of olaparib with SAE and AE information only being collected. No efficacy information will be required.

Patients on Cohort 1 may continue receiving olaparib as long as they are considered to be receiving benefit by the treating physician.

Patients on Cohort 2 may continue to receive olaparib in combination with paclitaxel for 6-9 cycles. At the discretion of the investigator, if the patient may benefit from continuing this treatment he/she may contact the AZ physician and discuss. If olaparib is not tolerated, patients may continue to receive the planned 6-9 cycles of paclitaxel (in total across Part A and B), after which the treatment will end. If paclitaxel is not tolerated but the investigator considers that the patient may benefit from switching to olaparib 300mg bd monotherapy dosing then he/she may contact the AZ physician and discuss the case. If it is agreed that the patient may benefit from switching to olaparib 300mg bd monotherapy then olaparib 300mg bd dose will be supplied for as long as they are considered to be receiving benefit from the drug, otherwise, the patient comes off the study immediately.

The study database will close to new data (data cut-off) 12 months after LSI and a CSR addendum issued. The study will then close.

Target subject population

Patients with advanced solid tumours, who are refractory or resistant to standard therapy and for whom no suitable effective standard therapy exists.

Investigational product, dosage and mode of administration

Olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain sufficient medication for at least each treatment period plus overage.

Olaparib will be supplied to the investigator as green film coated tablets containing 150mg or 100mg active. This will be administered at a dose of 300mg (Cohort 1) or 100mg (Cohort 2) orally twice daily, throughout each cycle (28 days) at the same times each day, with a glass of water (not exceed 240mL).

On the PK sample collection days of Part A, the patients should abstain from all food and drink (except water) at least 1 hour prior to study medication administration, and refrain from eating and drinking (except water) for a further 2 hours post dose. On non-PK sampling days, doses of olaparib may be taken at the same time as a light meal to assist in management of nausea/vomiting. However, this must be a light meal/snack only such as a couple of biscuits or a couple of slices of toast.

Comparator, dosage and mode of administration

Paclitaxel, 80mg/m^2 will be administered to patients in Cohort 2 only. This will be given as an intravenous (IV) infusion over 1 hour on Days 1, 8 and 15 of a 28-day cycle, and should be given one hour after the olaparib dose. Cycle 1 of paclitaxel treatment will commence after 8 days of multiple dosing of 100 mg bd olaparib monotherapy (to allow collection of a steady state olaparib monotherapy PK profile)

Paclitaxel should be sourced locally. Only under exceptional circumstances when this isn't feasible paclitaxel will be supplied through AstraZeneca.

Duration of treatment

All patients will undergo screening assessments during the maximum 28-day period preceding administration of the first dose of study drug.

Patients on Cohort 1, will be administered a single dose of olaparib 300mg monotherapy on Day 1 at the beginning of Part A period. On Day 2 and Day 3, no treatment will be given, but plasma PK samples will be obtained; after Day 3, the patients will be administered olaparib 300mg bd monotherapy treatment on a continuous schedule, ie, no break in olaparib dosing. Part A treatment will end after 8 days of multiple dose monotherapy treatment and Part B will start. Patients may continue receiving olaparib (300mg bd) until disease progression or as long as they are considered to be receiving benefit by the treating physician.

Patients on Cohort 2, will be administered a single dose of olaparib 100mg monotherapy on Day 1 at the beginning of Part A period. On Day 2 and Day 3, no treatment will be given, but plasma PK samples will be obtained; After Day 3, the patients will be administered olaparib 100mg bd monotherapy for a continuous 8-day schedule, followed by 100mg bd dose of olaparib given in combination with weekly paclitaxel (80 mg/m^2). Part A treatment will end after 1 cycle of combination treatment and Part B will start. Cycles are defined in 28-day periods to facilitate scheduling of visits and assessments. Patients are allowed to receive 6-9 cycles of paclitaxel and olaparib 100mg bd (in total across Part A and B). At the discretion of the investigator, if the patient may benefit from continuing this treatment he/she may contact the AZ physician and discuss. If olaparib is not tolerated, patients may continue to receive the planned 6-9 cycles of paclitaxel (in total across Part A and B), after which the treatment will end. If paclitaxel is not tolerated, at investigator's discretion that the patient may benefit from switching to olaparib 300mg bd monotherapy dosing then he/she may contact the AZ physician and discuss, otherwise, the patient comes off the study immediately.

Outcome variable(s):

- **Primary endpoints/variables**

Single dose PK parameters: C_{max}, t_{max}, $AUC_{(0-12)}$, AUC, Vd_{ss}/F, CL/F, kel, MRT, $t_{1/2}$.

Multiple dose PK parameters: $C_{max, ss}$, $C_{min, ss}$, $t_{max, ss}$, AUC_{ss}, Rac, DF, CL_{ss}/F, TCP.

Multiple dose parameters (in combination with paclitaxel): $C_{max, ss}$, $C_{min, ss}$, $t_{max, ss}$, AUC_{ss}, CL_{ss}/F.

- **Secondary endpoints/variables**

Incidence and severity of AEs and SAEs

Physical examination, ECOG performance status, vital signs including pulse and blood pressure, 12 lead ECGs, haematology, clinical chemistry, urinalysis, concomitant medications.

Ratio of steady state PK parameters ($C_{max, ss}$ ratio, $C_{min, ss}$ ratio, AUC_{ss} ratio) following dosing of olaparib in combination with paclitaxel: dosing olaparib alone

Statistical methods

The sample size for the study is 30 patients, dosed in two cohorts of 15 in order to obtain evaluable single and multiple dose pharmacokinetic data from 12 patients in each cohort. To be evaluable for pharmacokinetics analysis, the patient should comply with the study treatment scheme for Part A of the study and adhere to study restrictions.

No formal statistical analyses will be performed in this study. Summary measures of plasma concentrations across time and derived pharmacokinetic parameters will be produced. Safety and tolerability variables will also be summarized.

After the last patient has completed the treatment period in Part A, the database for Part A of the study will be locked, the PRIMA analysis will be performed and the part A data will be reported in a CSR. The end of Part B will be date of the earliest of the following events:

- 12 months after last subject in
- All patients have terminated from study in both cohorts
  - For Cohort 1, patients terminate from study when they discontinue olaparib, which can be taken until the investigator feels the patient is no longer benefiting from treatment
  - For Cohort 2, patients terminate from study when they have received 6-9 cycles of chemotherapy in combination with olaparib

At the end of Part B the final analysis containing subsequent safety assessments will be performed and will be presented in a CSR addendum.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADP	Adenosine diphosphate
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase (SGPT)
AML	Acute Myelocytic Leukemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate Transaminase (SGOT)
ATM	Ataxia-telangiectasia mutation
AUC	Area under plasma concentration-time curve from zero to infinity
$AUC_{(0-12)}$	Area under the curve from 0 to 12 hours post-dose
AUC_{ss}	Area under the curve during the dosing interval at steady state
AUMC	Area under the moment curve from time 0 to the time corresponding to the last measurable concentration
bd	Twice daily
BER	Base excision repair
BRCA	Breast cancer gene (type)
BP	Blood pressure
ºC	Degrees Celsius
%CV	Coefficient of variation
CI	Confidence interval
CL/F	Apparent Oral Clearance
C_{max}	Maximum plasma (peak) drug concentration after single dose administration
CL_{ss}	Total plasma clearance at steady state
$C_{max, ss}$	Maximum plasma concentration at steady state
$C_{min, ss}$	Minimum plasma concentration at steady state
CPU	Clinical Pharmacology Unit
cm	Centimetre

Abbreviation or special term	Explanation
CFDA	China Food and Drug Administration
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CT	Computerised Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CSA	Clinical Study Agreement
CSR	Clinical Study Report
dL	Decilitres
DNA	Deoxyribonucleic acid
DF	Degree of fluctuation
DAE	Discontinuation of Investigational Product due to Adverse Event
DCIS	Ductal carcinoma in situ
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECOG	Eastern Co-operative Oncology Group
FSH	Follicle stimulating hormone
%GCV	Geometric coefficient of variation
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GGT	Gamma glutamyltransferase
HDPE	High-density polyethylene
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HPMC	Hydroxypropyl Methylcellulose
HR	Hazard Ratio
HRD	Homologous recombination
HRT	Hormonal therapy
IC_{50}	Dose for 50% inhibition

Abbreviation or special term	Explanation
IRB	Institutional Review Board
ICH	International Conference on Harmonisation
INR	International Normalised Ratio
IP	Investigational Product
ITT	Intention to treat
IVRS	Interactive Voice Response System
IV	Intravenous
IWRS	Interactive Web Response System
Kel	Elimination rate constant
kg	Kilogram
LH	Luteinizing Hormone
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
LSI	Last Subject In
LSLV	Last Subject Last Visit
mg	milligram
MCHC	Mean cell haemoglobin concentration
MCH	Mean cell haemoglobin
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
OAE	Other Significant Adverse Event (see definition in Section 11.1.1)
ORR	Overall response rate
OS	Overall survival
od	Once daily
PAR	Poly-(ADP-ribose)
PARP	Poly (ADP-ribose) polymerase
PD	Progressive Disease
PFS	Progression-free survival
PK	Pharmacokinetics

Abbreviation or special term	Explanation
PLT	Pegylated liposomal doxorubicin
PO	Per oral
PR	The ECG interval measured from the beginning of the P wave to the beginning of the Q wave (or beginning of R wave if Q is missing).
PI	Principal Investigator
QRS	The ECG interval measured from the beginning of the Q wave (or the R wave if Q is missing) to the J point.
QT	The ECG interval measured from the beginning of the Q wave (or the R wave if Q is missing) to the end of the T wave.
R_{ac}	Accumulation ratio (index)
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
RR	The ECG interval between corresponding amplitude points of a QRS complex and the one preceding it
SAE	Serious adverse event (see definition in Section 6.3.2).
SAP	Statistical Analysis Plan
SD	Standard Deviation
ss	Steady state
$t_{½}$	Terminal half-life
t_{last}	Time at last measurable plasma concentration
t_{max}	Time of peak drug concentration
TCP	Temporal change parameter
µM	Micromolar
ULN	Upper limit of normal
V_{ss}/F or Vd_{ss}/F	Apparent volume of distribution at steady state
WBC	White Blood Cells
WBDC	Web Based Data Capture

1. INTRODUCTION

Olaparib (AZD2281, KU-0059436) is an inhibitor of PARP 1 and shows monotherapy activity in tumour cells with defective components of homologous recombination (HRD) pathway, which includes cells with the BRCA1-/- and BRCA2-/- genotype, as well as those with low

ataxia-telangiectasia mutation (ATM) gene expression (Hay et al 2005; Evers et al 2005; Rottenberg et al 2005). Due to the molecular targeting of olaparib to specific subsets of tumours, this has raised the opportunity for relatively less toxic cancer monotherapy using such a PARP 1 inhibitor compared with conventional treatments, such as chemotherapy.

1.1 Background

The capsule formulation was the original formulation for clinical studies; the majority of studies use this capsule formulation. The recommended monotherapy capsule dose is 400 mg bd. Olaparib (capsule) monotherapy appears to be generally well tolerated across studies at doses up to and including the MTD of 400 mg bd, which is 50mg/capsule, 8 capsules/per time, bd (Fong PC et al 2009; Fong PC et al 2010). A large number of capsules are therefore required to achieve a 400 mg bd daily dose (16 capsules per day), and consequently subject convenience may be compromised. As such, there are constraints associated with dosing subjects who require high doses of olaparib.

To alleviate the dosing constraints of the capsule formulation, AstraZeneca developed a melt-extrusion tablet (Melt-Extrusion [tablet] formulation) designed to deliver the therapeutic dose of olaparib in fewer and smaller dose units.

The recommended olaparib monotherapy tablet dose is 300 mg bd. The tablet formulation is considered to be a more patient friendly formulation for long term use requiring patients to take up to 2 tablets twice daily as compared to the capsule formulation requiring 8 capsules twice daily.

Currently, there are no data in Chinese. However, there are some data in Japanese patients. There was no evidence of any marked ethnic difference in the PK of olaparib between Japanese and Caucasian patients (Noboru Y, et al 2012). A population analysis of data obtained from capsule dosed monotherapy studies in the clinical programme has shown that patients age, body surface area, body weight, creatinine clearance or markers of hepatic function were not predictors of olaparib plasma exposure.

A Phase I, open-label study to assess the safety and tolerability of doses of olaparib tablet in Japanese patients with advanced solid malignancies is ongoing. The primary objective of this study is to investigate the safety and tolerability of olaparib tablet when given oral to Japanese patients with advanced solid malignancies. Based on the PK and safety data obtained from Study D0810C00024, 200 mg bd tablet dose is selected as the starting dose of this study.

The dose of olaparib will be escalated in Japanese patients and monitored for dose-limiting toxicity (DLT) to a dose level that is not higher than the defined Maximum tolerated dose (MTD) in a Western population.

Olaparib in capsule formulation as monotherapy has been investigated in 3 phase 2 studies in ovarian cancer patients, including Study D0810C00019, Study D0810C00012 and Study D0810C00041.

In Study D0810C00019 in patients with platinum sensitive relapsed serous ovarian cancer, progression free survival (PFS) following olaparib maintenance therapy was significantly longer compared with the placebo group. The hazard ratio (HR) was 0.35 (95% CI: 0.25, 0.49; p<0.00001). Median PFS was 8.4 months in the olaparib group compared with 4.8 months in the placebo group. In the subgroup of patients with BRCA mutant ovarian cancer, the HR was 0.18 (95% CI: 0.11, 0.31; p<0.00001; median 11.2 versus 4.3 months). An interim analysis of OS was performed at 58% maturity. In the overall population, the analysis demonstrated a non-statistically significant numerical advantage for olaparib-treated patients (OS HR 0.88; 95% CI 0.64-1.21; p=0.43808). In the BRCA-mutated subgroup, the non-statistically significant OS HR was 0.74 (95% CI 0.46 to 1.19; p=0.20813), with a numerical advantage in median overall survival observed with olaparib (median 34.9 months versus 31.9 months with placebo). Among the 62 placebo-treated patients with BRCA mutations, 14 switched to a PARP inhibitor post progression.

Study D0810C00012 was a Phase II open-label, randomized study to compare the efficacy and safety of olaparib with pegylated liposomal doxorubicin (PLD) in patients with gBRCA1 or gBRCA2 mutations and recurrent ovarian cancer (Stan et al 2012). Ninety-seven patients were enrolled and randomized in a 1:1:1 ratio to olaparib 200 mg bd or 400 mg bd continuously, or PLD 50 mg/m^2 intravenously, every 28 days. Results of the study showed that the efficacy of olaparib in patients with gBRCA1/gBRCA2 mutations and advanced ovarian cancer following a platinum-free interval of ≤12 months was not statistically different from the efficacy of PLD, but the CIs were wide and the point estimate favored olaparib (HR 0.88; 80% CI 0.62-1.28; p=0.6604). The response rate and PFS of olaparib 400 mg bd were consistent with previous studies, whereas for PLD these exceeded previously published data in patients with recurrent ovarian cancer.

Study D0810C00041 was a Phase II randomized study to investigate the efficacy and safety of olaparib in combination with carboplatin/paclitaxel followed by olaparib monotherapy as maintenance versus carboplatin/paclitaxel alone in patients with platinum-sensitive advanced serous ovarian cancer. Study results showed that there was a statistically significant improvement in PFS in the olaparib with carboplatin AUC4 + paclitaxel followed by olaparib maintenance arm compared to the control arm (HR=0.51; CI 0.34 to 0.77; p=0.0012). The median PFS was 12.2 months for the olaparib arm and 9.6 months for the control arm. Within the BRCA mutated subgroup, a significantly greater PFS benefit was observed for the olaparib arm compared with the control (HR: 0.21; 95% CI: 0.08-0.55; p= 0.0015). No statistically significant difference was seen between treatment arms in OS at the interim OS analyses (38% maturity; HR 1.37; 95% CI: 0.82 to 2.27); however, an imbalance between the arms in early censored patients (thought to be a consequence of the open label nature of the study) raises statistical concerns with the analyses.

Olaparib in capsule formulation as monotherapy has been investigated in 3 phase 2 studies in breast cancer patients, including Study D0810C00008, Study D0810C00020 and Study D0810C00042.

Study D0810C00008 was a Phase II proof-of-concept study initiated as an open-label, single-arm, international, multicenter study to assess the efficacy and safety of olaparib given orally bd in patients with advanced breast cancer (Andrew et al 2010). Patients had a median of 3 previous chemotherapy regimens. Approximately half of the patients had triple-negative breast cancer. The primary objective was to assess the efficacy of the capsule formulation at 2 different doses of olaparib in terms of ORR in patients with advanced breast cancer. Patients received olaparib at a dose of 400 mg bd or 100 mg bd continuously in 28-day cycles, for multiple cycles, until no further clinical benefit was apparent or the patient was withdrawn from the study. The cohorts were conducted in sequence, the 400 mg bd group first (n=27) followed by the 100 mg bd group (n=27). In the ITT analysis set, the confirmed Response Evaluation Criteria in Solid Tumors (RECIST) ORR overall was 11/27 (41%) at 400 mg bd and 6/27 (22%) at 100 mg bd. Responses were seen in both gBRCA1 and gBRCA2 carriers. Median time to progression was 5.3 months for the 400 mg bd group and 3.7 months for the 100 mg bd group.

Study D0810C00020 was a Phase II open-label, nonrandomized study of olaparib in patients with known gBRCA or high-grade serous/undifferentiated ovarian cancer and patients with known gBRCA or triple-negative breast cancer. All patients received olaparib 400 mg bd until disease progression or until the investigator believed it was in the best interest of the patient to stop treatment. Tumor response data was analysed in 64 ovarian (BRCA or serous ovarian) and 26 breast (BRCA or triple negative) cancer patients who received olaparib 400 mg bd. Median number of prior chemotherapies in the breast cancer group was 3 (range: 1 to 7). Over 70% of the breast cancer patients had received more than 3 previous lines of chemotherapy, with a median of 35.3 months from diagnosis to start of treatment with olaparib. None of the breast cancer patients achieved a RECIST response. However, 38.5% of patients had an overall best response of SD, and the median PFS was 1.8 months in this group.

Study D0810C00042 was a Phase II, open label, nonrandomized, noncomparative, multicenter study in patients with advanced cancers who had confirmed genetic BRCA1 and/or BRCA2 mutations. A total of 62 breast cancer patients were recruited, all of whom received at least 3 prior lines of therapy (with a median of 4 regimens). Eight (12.9%) of the breast cancer patients had an OR and the median duration of response was 204 days. At 16 weeks, disease control was observed in 23 (37.1%) patients. The median PFS was 3.68 months. The median OS was 11.01 months; the survival rate at 6 months was 74.6%, and at 1 year was 44.7%.

Olaparib tablet in combination with Paclitaxel has been investigated in one phase 2 study in gastric cancer patients, Study D0810C00039.

Study D0810C00039 (olaparib+paclitaxel in second-line gastric cancer) was a randomized Phase II study to compare the efficacy of olaparib tablets when given in combination with paclitaxel to paclitaxel alone, in the overall second-line gastric cancer population as well as the ataxia-telangiectasia mutated negative population. The study was enriched to include 50% patients classed as ATM negative, compared to a screening prevelance of 14% for ATM negative patients. The dose of olaparib was 100 mg bd and the dose of paclitaxel was 80 mg/m^2 given on Days 1, 8, and 15 of a 28-day cycle. A total of 123 patients were enrolled.

Study results showed that the effect on PFS was not statistically significant between the treatment arms (overall population PFS HR=0.80; 80% CI: 0.62, 1.03; 1-sided p-value=0.131). A statistically significant OS benefit was demonstrated for olaparib in combination with paclitaxel in the overall population (OS HR= 0.56; 80% CI: 0.41, 0.75; 1-sided p-value=0.005).

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Investigator's Brochure.

1.2 Research hypothesis

This study is a two part, phase I, open label study to determine the pharmacokinetics of olaparib in Chinese patients with advanced solid tumours.

1.3 Rationale for conducting this study

The pharmacokinetics, safety and tolerability data of olaparib capsule have been generated in Caucasian and Japan patients. The recommended monotherapy capsule dose is 400 mg bd. There was no evidence of any marked ethnic difference in the PK of olaparib between Japanese and Caucasian patients. The recommended olaparib monotherapy tablet dose is 300 mg bd. Based on preliminary data from an ongoing Phase I study (D0810C00024), the tolerability profile of the 300mg bd tablet dose is considered similar to the 400 mg bd capsule dose. A Phase I, open-label study to assess the safety and tolerability of doses of olaparib tablet in Japanese patients with advanced solid malignancies is ongoing.

This study is a two part, phase I, open label study to determine the pharmacokinetics of olaparib in Chinese patients with advanced solid tumours. The primary objective for this study is the characterisation of the pharmacokinetics of olaparib in Chinese patients following monotherapy doses of 300mg and 100mg, and following dosing at 100mg in combination with paclitaxel (dosed weekly at 80 mg/m^2 – days 1, 8 and 15 of a 28-day cycle).

This study is to be completed to support of the patient doses planned for the forthcoming Phase III ovarian and gastric cancer trials in Chinese patients (studies D0818C00001, D0818C00002 and D081BC00004). CFDA regulatory submissions for these studies are planned from August 2013 onwards.

1.4 Benefit/risk and ethical assessment

Approximately 5% of breast, ovarian and prostate cancer patients have inherited mutations of BRCA1 or BRCA2. In addition to genetic loss of BRCA function, it has been suggested that a further ~20% of tumours display so-called “BRCAness” (Narod and Foulkes 2004; Chan et al 2002). Furthermore, reduced function of other key proteins in the homologous recombination pathway similarly results in increased sensitivity to PARP inhibition and enhancement of chemotherapy and radiotherapy treatments. For these reasons, PARP inhibition represents a novel approach to anti-tumour therapy and may address an unmet need in patients with BRCA associated cancer. In addition, the use of PARPi in combination has confirmed that an enhancement of the anti-tumour activity of radiation and DNA damaging cytotoxic agents

occurs (Virag and Szabo 2002, Nguewa et al 2005). Identification of safe and effective doses of olaparib in combination regimens offers potential in many tumour types.

As of 22 February 2013, an estimated 1980 patients with ovarian, breast, pancreatic, gastric and a variety of other solid tumours are estimated to have received treatment with olaparib across the dose range 10 mg bd to 600 mg bd. Olaparib has been given as either monotherapy (14 studies, an estimated 1144 patients) or in combination with other chemotherapy/anti-cancer agents (eg, dacarbazine, gemcitabine, cisplatin, gemcitabine+cisplatin, topotecan, irinotecan, carboplatin and/or paclitaxel, paclitaxel, bevacizumab, liposomal doxorubicin, irinotecan+cisplatin+mitomycin C, or temozolomide) (21 studies, an estimated 836 patients). The majority of patients to date have received the capsule formulation of olaparib (an estimated 1574 patients). Approximately 406 patients have received the tablet formulation to date. Approximately 304 patients have received comparator or placebo across the olaparib development programme.

Data from the available pre-clinical studies and subsequent clinical development programme demonstrate that olaparib appears to be active and generally well tolerated in patients with solid tumours including those with BRCA mutated cancers. In ovarian cancer, responses have been seen in all patient groups, including platinum resistant and refractory cancer.

From the available data to date in patients with advanced cancer, there is no evidence of any unexpected toxicity following long-term olaparib capsule monotherapy exposure. Adverse laboratory findings and/or clinical diagnoses considered to be associated with administration of olaparib monotherapy include haematological effects (anaemia, neutropenia, lymphopenia, thrombocytopenia, MCV elevation), nausea and vomiting, diarrhoea, dyspepsia, dysgeusia, fatigue (including asthenia), headache and dizziness. Most of these events were generally mild or moderate in intensity. Pneumonitis events with no consistent clinical pattern have been reported in a small number of patients. Myelodysplastic syndrome/AML have been reported in a small number of patients generally with extensive previous exposure to chemotherapy. Preliminary data from Phase I dose escalation studies of olaparib in combination with various chemotherapy agents indicate an increase in bone marrow toxicity (anaemia, neutropenia, thrombocytopenia) greater than expected if the agents had been administered alone. The effects are generally transient but treatment delays are common

Olaparib (in the capsule formulation) appears to be generally well tolerated in patients with various solid tumours at doses up to and including 400 mg bd, as monotherapy. The tolerability profile of the 300mg bd tablet dose has been shown to be similar to the 400 mg bd capsule dose. In addition, in study D0810C00039, overall Olaparib tablet 100mg bd in combination with weekly paclitaxel 80mg/m^2 was well tolerated, with no new unexpected safety findings. In this study, the same combination regimen will be used in Cohort 2 patients.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

Primary Objectives

- To characterize the single dose pharmacokinetics of olaparib following a 300mg monotherapy dose and a 100mg monotherapy dose in Chinese patients.
- To characterize the steady state pharmacokinetics of olaparib following 300mg bd monotherapy dose, 100mg bd monotherapy dose and 100mg bd dose of olaparib given in combination with weekly paclitaxel (80 mg/m^2)

Secondary Objectives

- To determine the safety and tolerability of olaparib when given as monotherapy (300mg bd) and in combination with paclitaxel (100mg bd olaparib plus 80 mg/m^2) in patients with advanced solid tumours.
- To explore the effect of co-administration of paclitaxel (80 mg/m^2) on steady state exposure to olaparib (100 mg bd).

2.2 Endpoints

Primary Endpoints

- Single dose PK parameters: C_{max}, t_{max}, $AUC_{(0-12)}$, AUC, Vd_{ss}/F, CL/F, kel, MRT, $t_{1/2}$.
- Multiple dose PK parameters: $C_{max, ss}$, $C_{min, ss}$, $t_{max, ss}$, AUC_{ss}, Rac, DF, CL_{ss}/F, TCP
- Multiple dose parameters (in combination with paclitaxel): $C_{max, ss}$, $C_{min, ss}$, $t_{max, ss}$, AUC_{ss}, CL_{ss}/F.

Secondary Endpoints

- Incidence and severity of AEs and SAEs
- Physical examination, ECOG performance status, vital signs including pulse and blood pressure, 12 lead ECGs, haematology, clinical chemistry, urinalysis, concomitant medications.
- Ratio of steady state PK parameters ($C_{max, ss}$ ratio, $C_{min, ss}$ ratio, AUC_{ss} ratio) following dosing of olaparib in combination with paclitaxel: dosing olaparib alone

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

This is a phase I, open label, two part study (Part A and Part B) to determine the pharmacokinetics of olaparib 300 mg bd administered as monotherapy and olaparib 100 mg bd as monotherapy and in combination with paclitaxel (100mg bd olaparib plus weekly 80mg/m^2 paclitaxel), in Chinese patients with advanced solid tumours.

Approximately 30 patients will enter into this study, with 15 patients enter into each of two treatment cohorts (Cohort 1 and Cohort 2). The execution of Cohort 2 can be conducted in parallel with Cohort 1.

Part A will assess the pharmacokinetics of olaparib:

- Cohort 1 will investigate the single and multiple dose pharmacokinetics of olaparib following 300mg bd monotherapy dose(s)

- Cohort 2 will investigate the single and multiple dose pharmacokinetics of olaparib following 100mg bd monotherapy dose(s) and the multiple dose pharmacokinetics in the presence of co-administered paclitaxel (80mg/m^2 weekly on days 1, 8 and 15 of a single 28-day cycle).

Part B will assess the safety of olaparib with SAE and AE information only being collected. No efficacy information will be required:

- Patients in Cohort 1 may continue receiving olaparib as long as they are considered to be receiving benefit by the treating physician.

- Patients on Cohort 2 may continue to receive olaparib in combination with paclitaxel for 6-9 cycles. At the discretion of the investigator, if the patient may benefit from continuing this treatment he/she may contact the AZ physician and discuss. If olaparib is not tolerated, patients may continue to receive the planned 6-9 cycles of paclitaxel (in total across Part A and B), after which the treatment will end. If paclitaxel is not tolerated but the investigator considers that the patient may benefit from switching to olaparib 300mg bd monotherapy dosing then he/she may contact the AZ physician and discuss the case. If it is agreed that the patient may benefit from switching to olaparib 300mg bd monotherapy then olaparib 300mg bd dose will be supplied for as long as they are considered to be receiving benefit from the drug, otherwise, the patient comes off the study immediately.

3.1 Overall study design and flow chart

Figure 1 Study Schema-Cohort 1: Olaparib 300 mg Monotherapy

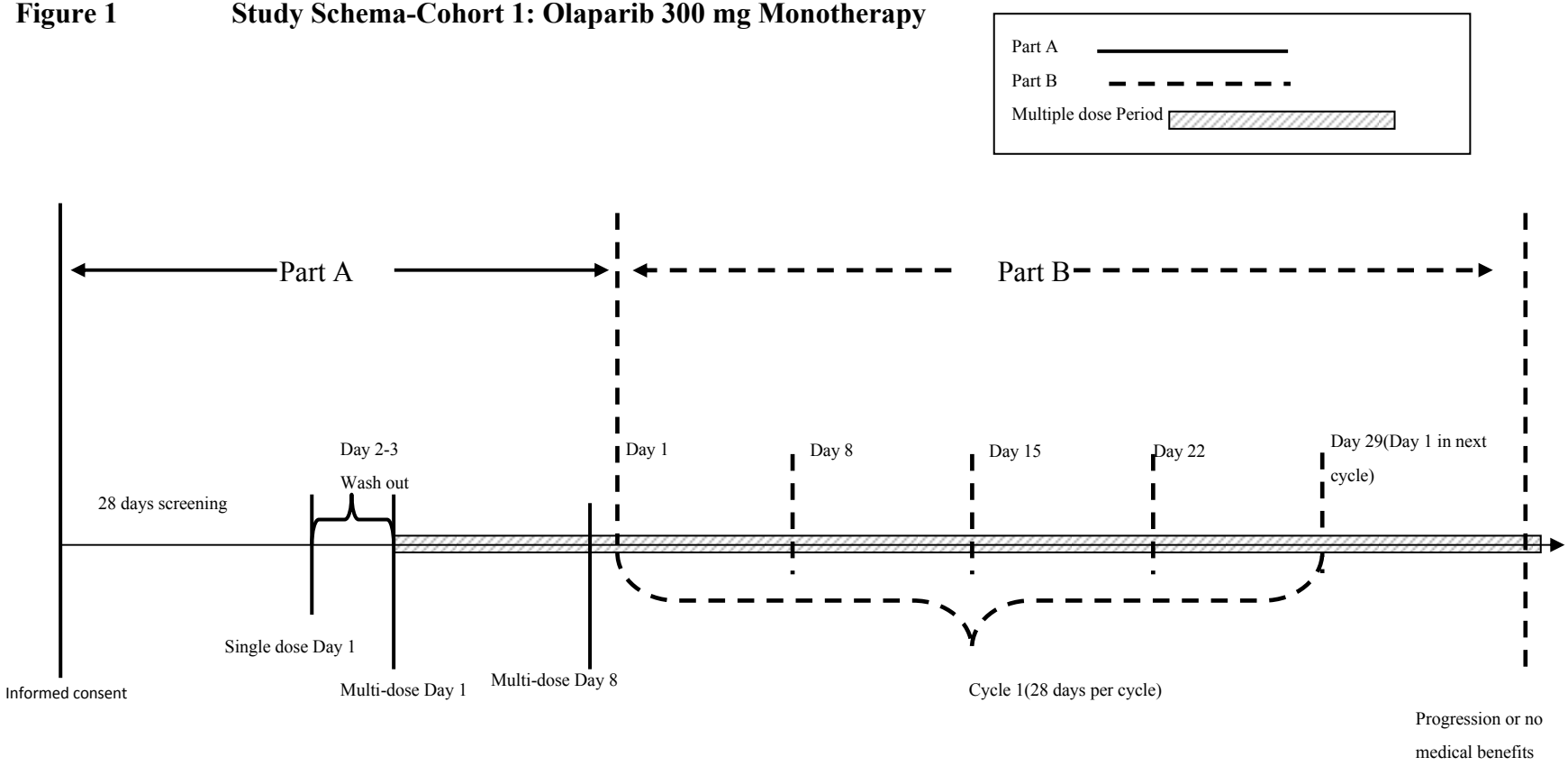

Figure 2 Study Schema-Cohort 2: Olaparib 100mg bd in Combination with Paclitaxel

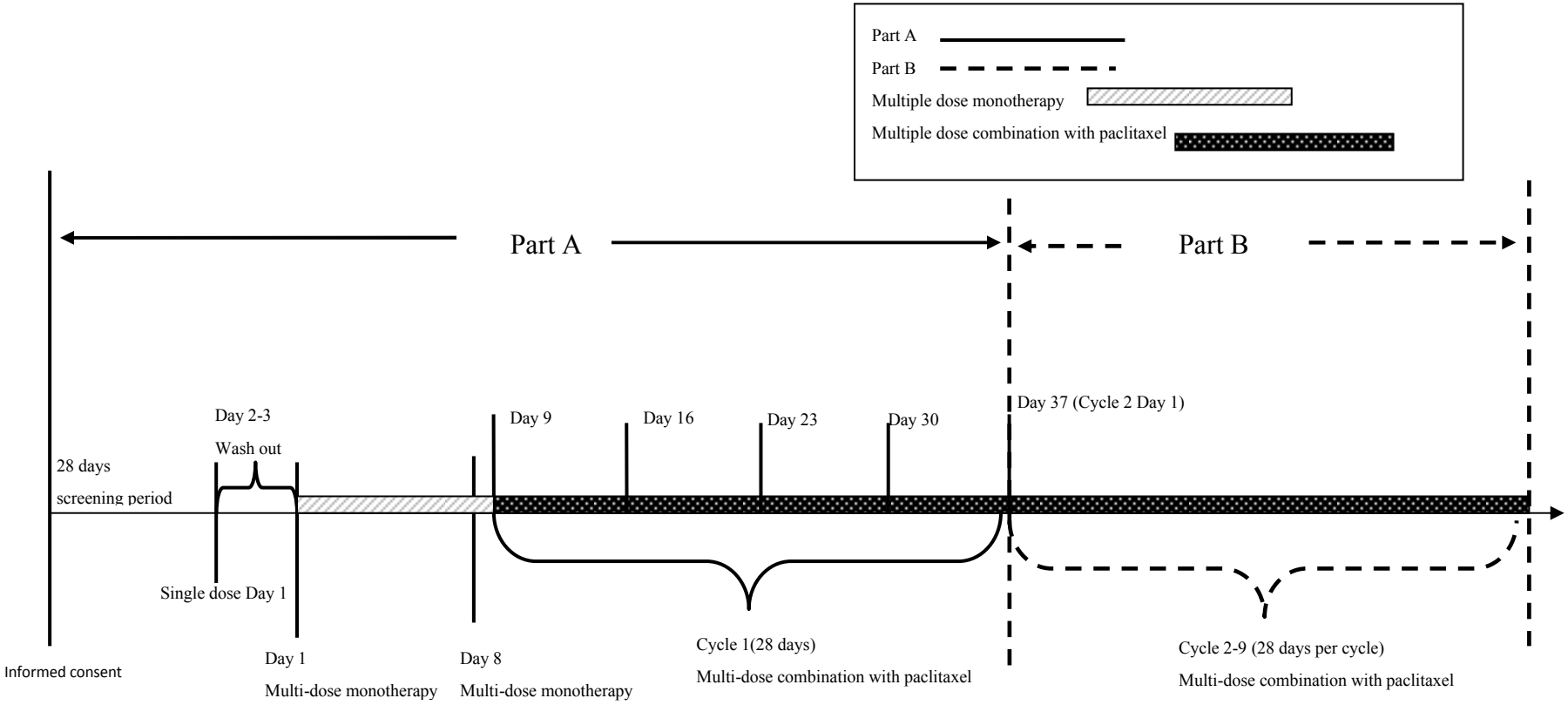

Table 1 Study Schedule – Cohort 1 Patients (300mg bd Monotherapy Dose)

Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Subsequent On-Treatment Visits (every 4 weeks[g] Visit 11 onwards)**	**Study Treatment Discontinued**	**Follow Up (30 days after last dose of study medication)**
	Screening	**Part A**					**Part B**							
		Single Dose Period			**Multiple Dose Period**									
Day	**-28 to -1**	**1**	**2**	**3**	**1**	**8**	**1**	**8**	**15**	**22**	**29**	**Day 57, Day 85 etc.**		
Visit Window								**±3d**	**±3d**	**±3d**	**±3d**	**±7d**		**±7d**
Inclusion/Exclusion Criteria	X													
Informed Consent	X													
Demographics	X													
Medical and Surgical History	X													
Physical Examination	X	X[a]			X		X				X	X	X	X
Vital Signs, Body Weight, Height[h] (Includes BP [Supine	X	X			X	X	X	X	X	X	X	X	X	X

Table 1 Study Schedule – Cohort 1 Patients (300mg bd Monotherapy Dose)

Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Subsequent On-Treatment Visits (every 4 weeks[g] Visit 11 onwards)**	**Study Treatment Discontinued**	**Follow Up (30 days after last dose of study medication)**
	Screening	**Part A**					**Part B**							
		Single Dose Period			**Multiple Dose Period**									
Day	**-28 to -1**	**1**	**2**	**3**	**1**	**8**	**1**	**8**	**15**	**22**	**29**	**Day 57, Day 85 etc.**		
Visit Window								**±3d**	**±3d**	**±3d**	**±3d**	**±7d**		**±7d**
Position], Pulse and Temperature														
ECOG Performance Status	X	X			X		X				X	X	X	X
ECG	X	X[a]			X		X				X	X		X
Haematology/Clinical Chemistry/Urinalysis	X	X[b]			X	X	X	X	X	X	X	X	X	X
Serology Test (Hepatitis B surface antigen; Anti HCV IgG;	X													

Table 1 Study Schedule – Cohort 1 Patients (300mg bd Monotherapy Dose)

Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Subsequent On-Treatment Visits (every 4 weeks[g] Visit 11 onwards)**	**Study Treatment Discontinued**	**Follow Up (30 days after last dose of study medication)**
	Screening	**Part A**					**Part B**							
		Single Dose Period			**Multiple Dose Period**									
Day	**-28 to -1**	**1**	**2**	**3**	**1**	**8**	**1**	**8**	**15**	**22**	**29**	**Day 57, Day 85 etc.**		
Visit Window								**±3d**	**±3d**	**±3d**	**±3d**	**±7d**		**±7d**
HIV)														
Pregnancy Test	X	X												
Olaparib Dispensed/Returned		X			X		X				X	X		
Olaparib Dosing		X[c]			X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]		
Blood for PK		X[e]	X[e]	X[e]		X[f]								
Adverse Events (from time of consent)	X	→	→	→	→	→	→	→	→	→	→	→	→	X
Concomitant Medications	X	→	→	→	→	→	→	→	→	→	→	→	→	X

a If being assessed within 7 days before first dosing of study medication, it may not be repeated on Day 1 of Part A

b The lab safety assessments may not need to be repeated on Day 1 of Part A if these tests are performed on Day -2 or Day -1 during Screening.

c Single 300 mg dose (2 × 150 mg tablet) administered only
d Twice daily 300 mg dose
e PK samples to be collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 (Day 2) and 48 h (Day 3)
f PK samples to be collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6,8 and 12 h post dose
g Visit to take place on Day 1 of a 4 week (28 days) visit period. Visits will continue for 12 months post Last Subject In (LSI)
h Height to be done at screening only

Table 2 Study Schedule – Cohort 2 Patients (100mg bd Monotherapy Dose, Followed by 100mg bd Monotherapy + Weekly Paclitaxel)

Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Subsequent On-Treatment Visits (on a weekly basis Visit 14 onwards)**	**Study Treatment Discontinued**	**Follow Up (30 days after last dose of study medication)**
	Screening	**Part A**									**Part B**						
		Single Dose Monotherapy Period			**Multiple Dose Monotherapy Period**		**Multiple Dose Combination Period (Cycle 1 paclitaxel treatment)**				**Multiple Dose Combination Period (Cycles 2-9 paclitaxel treatment)**						
Day	**-28 to -1**	**1**	**2**	**3**	**1**	**8**	**9**	**16**	**23**	**30**	**37**	**44**	**51**	**58**	**Day 65, Day 72 etc.**		
Visit Window								**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d[f]/±3d[f]**		**±7d**
Inclusion/Exclusion Criteria	X																
Informed Consent	X																
Demographics	X																
Medical and Surgical History	X																
Physical Examination	X	X[a]			X		X				X				X[b]	X	X
Vital Signs, Body weight, Height[i] (Includes BP [Supine Position], Pulse and	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2 Study Schedule – Cohort 2 Patients (100mg bd Monotherapy Dose, Followed by 100mg bd Monotherapy + Weekly Paclitaxel)

Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Subsequent On-Treatment Visits (on a weekly basis Visit 14 onwards)**	**Study Treatment Discontinued**	**Follow Up (30 days after last dose of study medication)**
	Screening	**Part A**									**Part B**						
		Single Dose Monotherapy Period			**Multiple Dose Monotherapy Period**		**Multiple Dose Combination Period (Cycle 1 paclitaxel treatment)**				**Multiple Dose Combination Period (Cycles 2-9 paclitaxel treatment)**						
Day	**-28 to -1**	**1**	**2**	**3**	**1**	**8**	**9**	**16**	**23**	**30**	**37**	**44**	**51**	**58**	**Day 65, Day 72 etc.**		
Visit Window								**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d[f]/±3d[f]**		**±7d**
Temperature																	
ECOG Performance Status	X	X			X		X				X				X[b]	X	X
ECG	X	X[a]			X		X				X				X[b]		X
Haematology/Clinical Chemistry/Urinalysis	X	X[c]			X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X	X															
Serology Test (Hepatitis B surface antigen; Anti HCV IgG; HIV)	X																

Table 2 Study Schedule – Cohort 2 Patients (100mg bd Monotherapy Dose, Followed by 100mg bd Monotherapy + Weekly Paclitaxel)

Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Subsequent On-Treatment Visits (on a weekly basis Visit 14 onwards)**	**Study Treatment Discontinued**	**Follow Up (30 days after last dose of study medication)**
	Screening	**Part A**									**Part B**						
		Single Dose Monotherapy Period			**Multiple Dose Monotherapy Period**		**Multiple Dose Combination Period (Cycle 1 paclitaxel treatment)**				**Multiple Dose Combination Period (Cycles 2-9 paclitaxel treatment)**						
Day	**-28 to -1**	**1**	**2**	**3**	**1**	**8**	**9**	**16**	**23**	**30**	**37**	**44**	**51**	**58**	**Day 65, Day 72 etc.**		
Visit Window								**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d[f]/±3d[f]**		**±7d**
Olaparib Dispensed/Returned		X			X		X				X				X[b]		
Olaparib Dosing		X[d]			X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]		
Paclitaxel Infusion							X	X	X		X	X	X		X[f]		
Blood for PK		X[g]	X[g]	X[g]		X[h]	X[h]										
Adverse Events (from time of consent)	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Concomitant Medications	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X

a If being assessed within 7 days before first dosing of study medication, it may not be repeated on Day 1 of Part A
b The assessment/procedure to be performed only on Day 1 of each cycle during the multiple dose combination period in Part B.

c The lab safety assessments may not need to be repeated on Day 1 of Part A if these tests are performed on Day -2 or Day -1 during Screening.

d Single 100 mg dose (1 × 100 mg tablet) administered only

e Twice daily 100 mg dose

f The paclitaxel to be dosed weekly at 80 mg/m^2 on Days 1, 8 and 15 of a 28-day cycle during the multiple dose combination period. The visit window for the paclitaxel dosing days in each cycle is ± 1day (except for first dosing of paclitaxel i.e. Day 9), for the non-dosing visit day in the cycle, the visit window is allowed Scheduled visit ± 3 days.

g PK samples to be collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 (Day 2) and 48 h (Day 3)

h PK samples to be collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12h post morning olaparib dose on each of these days

i Height to be done at screening only

3.2 Rationale for study design, doses and control groups

The primary objective of this study is to characterize the single dose pharmacokinetics in Chinese patients following dosing of a 300mg monotherapy and a 100mg monotherapy dose of olaparib, and to characterize steady state pharmacokinetics of olaparib following a 300mg bd monotherapy dose, a 100mg bd monotherapy dose and a 100mg bd dose of olaparib in combination with weekly paclitaxel (80mg/m^2).

Based on the preliminary result of the ongoing phase 1 study D0180C00024, 300mg is the recommended dose for olaparib tablets as monotherapy in the phase 3 studies in the ovarian cancer patients. In the phase 3 studies in gastric cancer, an olaparib tablet dose of 100mg in combination with weekly paclitaxel 80mg/m^2 is recommended dose. The doses of olaparib monotherapy and in combination with paclitaxel are therefore consistent with those being used in the phase 3 trials.

4. SUBJECT SELECTION CRITERIA

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1. Provision of fully informed consent prior to any study specific procedures

2. Patient aged ≥ 18 years

3. Histologically or, where appropriate, cytologically confirmed malignant solid tumour refractory or resistant to standard therapy and for which no suitable effective standard therapy exists

4. Patients must have a life expectancy of ≥ 12 weeks

5. Patients for Cohort 2 must be eligible for paclitaxel treatment

6. Patients are willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations

7. ECOG performance status ≤ 2 (see Appendix G)

8. Patients must have satisfactory organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:

- Haemoglobin ≥ 10.0 g/dL and no blood transfusion in the 4 weeks prior to the first dosing of study drug.
- Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
- White blood cells (WBC) > 3×10^9/L
- Platelet count ≥ 100×10^9/L
- Total bilirubin ≤ 1.5 × institutional upper limit of normal
- AST (SGOT)/ALT (SGPT) ≤ 2.5 × institutional upper limit of normal unless liver metastases are present in which case it must be ≤ 5× ULN
- Serum creatinine ≤ 1.5 × institutional upper limit of normal (ULN)
- Calculated serum creatinine clearance >50 ml/min (using Cockroft Gault formula or 24 hour urine collection)

9. Evidence of non-childbearing status for women of childbearing potential, or postmenopausal status: negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on Day 1. Postmenopausal is defined as:
   - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments,
   - LH and FSH levels in the post menopausal range for women under 50,
   - Radiation-induced oophorectomy with last menses >1 year ago,
   - Chemotherapy-induced menopause with >1 year interval since last menses,
   - Or surgical sterilisation (bilateral oophorectomy or hysterectomy).
10. Patients must be on a stable concomitant medication regimen, defined as no changes in medication or in dose within 2 weeks prior to start of olaparib dosing, except for bisphosphonates, denosumab and corticosteroids, which should be stable for at least 4 weeks prior to start of olaparib dosing

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

2. Previous enrolment in the present study.

3. Treatment with any investigational product during the last 14 days (or a longer period depending on the defined characteristics of the agents used).

4. Any previous treatment with a PARP inhibitor, including olaparib.

5. Patients with other malignancy within the last 5 years, except adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, Grade 1 endometrial cancer, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years.

6. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication. These include patients with gastric or intestinal cancer or patients with prior surgical procedures such as full or partial gastrectomy.

7. Patients receiving any systemic chemotherapy, radiotherapy (except for palliative reasons), within 4 weeks from the last dose prior to study treatment (or a longer period depending on the defined characteristics of the agents used). The patient can receive a stable dose of bisphosphonates for bone metastases, before and during the study as long as these were started at least 4 weeks prior to treatment.

8. Concomitant use of known potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir.

9. Patients with any ongoing toxicities (>CTCAE grade 2), with the exception of alopecia, caused by previous cancer therapy.

10. Resting ECG with QTc > 470msec on 2 or more time points within a 24 hour period or family history of long QT syndrome.

11. Patients with interstitial pneumonia or diffused symptomatic fibrosis of the lungs.

12. Patients with myelodysplastic syndrome/acute myeloid leukaemia.

13. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment.

14. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

15. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.

16. Immunocompromised patients, e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV).

17. Patients with known active hepatic disease (i.e. Hepatitis B or C).

18. Patients with a known hypersensitivity to olaparib, paclitaxel or any of the excipients of the product.

19. Breastfeeding women.

20. Clinical judgement by the investigator that the patient should not participate in the study.

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

1. Female patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for at least 1 month after last dose of study drug(s)

   Male patient Male patients and their partners, who are sexually active and of childbearing potential, must agree to the use of TWO highly effective forms of contraception in combination, throughout the period of taking study treatment and for 3 months after last dose of study drug(s), including:

   - Condom with spermicide

   And one of the following:

   - Oral contraceptive or hormonal therapy (e.g. hormone implants)
   - Placement of an intra-uterine device

   Appendix E provides details of acceptable birth control methods to be used within the study.

2. No other chemotherapy, or other novel agent is to be permitted during the course of the study treatment for any patient (the patient can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to treatment, as per exclusion criteria above).

3. Live virus and bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

4. Patients should avoid concomitant use of drugs and herbal supplements known to modulate CYP3A4 enzyme activity from the time they enter the screening period until 30 days after the last dose of study medication. In vitro data have shown that the principal enzyme responsible for the formation of the three main metabolites of olaparib is CYP3A4 and consequently, this restriction is required to ensure patient safety. (Appendix D provides the List of drugs that may have potential CYP3A4 interactions.)

5. Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.

5.2 Subject enrolment

The Investigator will:

- Obtain signed informed consent from the potential subjects before any study-specific procedure is performed.
- Assign potential subject a unique enrolment number, beginning with ‘E0001001’.
- Determine subject eligibility. See Sections 4.1and Section 4.2.
- Assign eligible subject a unique subject number, beginning with ‘1001’for Cohort 1 patients and ‘2001’ for Cohort 2 patients.

Subjects will be enrolled into the study provided they have satisfied all subject selection criteria.

If subjects have withdrawn their participation in the study after dosing they cannot re-enter into the study.

If a subject withdraws his/her participation in the study, then his/her enrolment code cannot be reused.

5.3 Procedures for handling subjects incorrectly enrolled

Subjects who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Where a subject, who does not meet the selection criteria, is enrolled in error and this is identified before dosing, the subject should be withdrawn from the study. A discussion should occur between the AstraZeneca Study Team Physician and the investigator regarding whether a replacement may be considered.

Where a subject, who does not meet the selection criteria, is enrolled in error and started on treatment, or where a subject subsequently fails to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Team Physician and the investigator regarding whether to continue or discontinue the subject from treatment. If treatment is discontinued the subject should be advised to continue assessments to ensure their safety. In situations where an agreement cannot be reached, the subject should have their study treatment discontinued.

The AstraZeneca Study Team Physician is to ensure all decisions are appropriately documented.

5.4 Blinding and procedures for unblinding the study-Not applicable

The study will be open-label.

5.5 Treatments

5.5.1 Identity of investigational product(s)

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply the olaparib to the Investigator as green film-coated tablets as shown in Table 3.

Table 3 Investigational Product(s)

Investigational product	Dosage form and strength
Olaparib	100 mg Tablets
Olaparib	150 mg Tablets

Paclitaxel should be sourced locally. Only under exceptional circumstances when this isn't feasible paclitaxel will be supplied through AstraZeneca.

Descriptive information for paclitaxel can be found in the local package insert supplied with the drug.

5.5.2 Doses and treatment regimens

For all centres, olaparib will be packed in high density polyethylene (HDPE) bottles with child-resistant closures. The study treatment will be dispensed to patients. Each dosing container will contain sufficient medication for at least each treatment period plus overage. Multiple bottles of olaparib may be required for dispensing in order to make up the desired dose.

Olaparib is available as a green film-coated tablet containing 150 mg or 100 mg. Patients on Cohort 1 will receive 300 mg olaparib comprised of 2 ×150 mg tablets.

During the multiple dose treatment period, doses of study treatment should be taken at the same times each day approximately 12 hours apart. All doses should be taken with approximately 240ml of water.

On the PK sample collection days of Part A, the patients should abstain from all food and drink (except water) at least 1 hour prior to study medication administration, and refrain from eating and drinking (except water) for a further 2 hours post dose. For non-PK sampling days, doses of olaparib may be taken as a light meal to assist in management of nausea/vomiting. However, this must be a light meal/snack only such as a couple of biscuits or a couple of slices of toast.

The olaparib tablets must be taken intact. It should not be bitten, chewed, cut, or otherwise altered prior to swallowing. Subjects not swallowing the medication whole will be considered non-compliant and should be discontinued.

During Part A treatment period, any patient that vomits within 3 hours after dosing will be considered non-evaluable for PK analysis set and will come off the study treatment, unless after discussion between the investigator and the AZ physician, it is agreed that the patient may benefit from treatment and can transfer to Part B of the study. Any patient that vomits more than 3 hours after dosing will be still considered evaluable for PK set analysis.

During the Part B treatment, if vomiting occurs shortly after the study treatment tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Combination Treatment

Paclitaxel, 80mg/m^2 will be administered to patients in Cohort 2 only. This will be given as an intravenous (IV) infusion over 1 hour on Days 1, 8 and 15 of a 28-day cycle, and should be given one hour after the olaparib dose. Cycle 1 of paclitaxel treatment will commence after 8 days of multiple dosing of 100 mg bd olaparib monotherapy (to allow collection of a steady state olaparib monotherapy PK profile).

Treatment Duration

Patients on Cohort 1, will be administered a single dose of olaparib 300mg monotherapy on Day 1 at the beginning of Part A period. On Day 2 and Day 3, no treatment will be given, but plasma samples will be obtained; after Day 3, the patients will be administered olaparib 300mg bd monotherapy on a continuous schedule, ie, no break in olaparib dosing. Part A treatment will end after 8 days of multiple dose treatment and Part B will start. Patients may continue receiving olaparib (300mg bd) until objective progression or as long as they are considered to be receiving benefit by the treating physician.

Patients on Cohort 2, will be administered a single dose of olaparib 100mg on Day 1 at the beginning of Part A period. On Day 2 and Day 3, no treatment will be given, but plasma samples will be obtained; After Day 3, the patients will be administered olaparib 100mg bd monotherapy for a continuous 8-day schedule, followed by 100mg bd dose of olaparib given in combination with weekly paclitaxel (80 mg/m^2). Part A treatment will end after 1 cycle of combination treatment and Part B will start. Cycles are defined in 28-day periods to facilitate scheduling of visits and assessments. Patients are allowed to receive 6-9 cycles of paclitaxel and olaparib 100mg bd (in total across Part A and B). At the discretion of the investigator, if the patient may benefit from continuing this treatment he/she may contact the AZ physician and discuss. If olaparib is not tolerated, patients may continue to receive the planned 6-9 cycles of paclitaxel (in total across Part A and B), after which the treatment will end. If paclitaxel is not tolerated, at investigator's discretion that the patient may benefit from switching to olaparib 300mg bd dosing then he/she may contact the AZ physician and discuss, otherwise, the patient comes off the study immediately.

Premedications for paclitaxel treated patients

Patients on Cohort 2, should be premedicated (as per local standard practice) prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel. These premedications should be sourced locally.

5.5.3 Management of toxicity

In Part A for both Cohort 1 and Cohort 2, no dose reduction is allowed, if the patient is not well tolerated to the treatment during this period, the patient should withdraw.

Patients on Cohort 1:

In Part B, any toxicity observed during this period will be managed by interruption of olaparib, as deemed appropriate by the Investigator. Repeat dose interruptions are allowed as required, for a maximum of 14 days on each occasion. If the interruption is any longer than this the AstraZeneca study team must be informed. Study treatment must be interrupted until the patient recovers completely or the toxicity reverts to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (Version 4) grade 1 or less.

Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of study treatment.

Management of anaemia:

Adverse events of anaemia CTCAE grade 1 or 2 (Haemoglobin (Hb) $\geq$ 8 g/dl) should be investigated and managed as deemed appropriate by the investigator with or without interruption of study drug or change in dose, taking into account previous history of anaemia. Common treatable causes of anaemia (e.g. iron, vitamin B12 or folate deficiencies and hypothyroidism) should be excluded. In some cases management of anaemia may require blood transfusions. However, if patient develops anaemia CTCAE grade 3 (Hb < 8g/dl) or worse, study treatment should be interrupted for up to maximum of 4 weeks to allow for bone marrow recovery and patient should be managed appropriately. Study treatment can be restarted at the same dose if Hb has recovered to $\geq$ 9 g/dl. Any subsequently required anaemia related interruptions, considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require study treatment dose reductions to 250 mg bd as a first step and to 200 mg bd as a second step.

If a patient has been treated for anaemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependant as judged by investigator, study treatment should be interrupted for up to a maximum of 4 weeks to allow for bone marrow recovery. Study treatment should be restarted at a reduced dose.

Management of neutropenia and leukopenia:

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h of the last dose of study treatment.

Study treatment can be restarted at the same dose if an adverse event of neutropenia or leucopenia have been recovered up to CTCAE grade $\geq$1 (ANC $\geq 1.5 \times 10^9$/L). Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF).

Any subsequent interruptions will require study treatment dose reductions to 250 mg bd as a first step and to 200 mg bd as a second step.

Management of thrombocytopenia

An adverse event of thrombocytopenia should be managed as deemed appropriate by the investigator. If patient develops thrombocytopenia CTCAE grade 3 or worse study treatment should be interrupted for a max of 4 weeks. In some cases management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.

Management of prolonged haematological toxicities while on study treatment:

If patient develops prolonged haematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC $< 1 \times 10^9$/L)
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia (Platelets $< 50 \times 10^9$/L)

Weekly differential blood counts including reticulocytes (calculate reticulocyte index (RI), RI = reticulocyte count x haematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct) (1,2) and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the Investigator to AstraZeneca Patient Safety. Study treatment should be discontinued if diagnosis of myelodysplastic syndrome is confirmed.

Management of new or worsening pulmonary symptoms:

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in study treatment dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Study Physician.

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. They are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter in accordance with local treatment practice guidelines.

Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with AstraZeneca study physician.

If a patient discontinues treatment for intercurrent condition and progresses while off treatment, they can restart study treatment if the investigator feels the patient is receiving clinical benefit. Please note that evidence of objective radiological disease progression is required.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Table 4 Dose Reductions for Patients on Cohort 1 During Part B Treatment

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300mg[a]	250mg[α, b]	200mg[α, b]

a 300 mg olaparib comprises of 2 × 150 mg tablets; 250 mg comprises of 1 × 150mg tablet and 1 × 100 mg tablet; 200 mg comprises of 2 × 100 mg tablets.
b Dose must not be re-escalated even if toxicities have resolved.

Patients on Cohort 2:

No dose reduction is allowed in Part A.

In Part B, if olaparib is not tolerated, patients may continue to receive the planned 6-9 cycles of paclitaxel (in total across Part A and B), after which the treatment will end. If paclitaxel is not tolerated but the investigator considers that the patient may benefit from switching to olaparib 300mg bd monotherapy dosing then he/she may contact the AZ physician and discuss the case. If it is agreed that the patient may benefit from switching to olaparib 300mg bd monotherapy then olaparib 300mg bd dose will be supplied for as long as they are considered to be receiving benefit from the drug, otherwise, the patient comes off the study immediately. For patients who switch to 300mg bd monotherapy, the Management of Toxicity will follow Cohort 1.

Each patient should receive three paclitaxel doses in a four-week period as toxicity permits however interruption or dose modification of paclitaxel must follow labelled recommendations where appropriate (for example, myelosuppression). Interruption of olaparib for paclitaxel-specific toxicities (for example, peripheral neuropathy) should be avoided.

Treatment with paclitaxel may continue at the full dose of 80 mg/m^2 (unless previously dose reduced) on Days 1, 8 and 15 of each cycle as long as the following criteria are met, else paclitaxel should be held until restoration of ANC and platelet count:

- ANC $\geq 1.5 \times 10^9$/L
- Platelets $\geq 100 \times 10^9$/L

In the event that a patient has not recovered sufficiently to enable the next chemotherapy cycle to start, then the cycle should be delayed until the toxicity has recovered sufficiently to allow further dosage. The maximum cycle delay permitted is 28 days. In the event that only the paclitaxel needs to be held and the patient is still receiving continuous dosing of olaparib, then the start of the chemotherapy cycle should be delayed, however the patient should continue the olaparib doses during the delay period, unless any other criteria requires doses to be omitted.

Further dose modifications are described in Table 5, Table 6 and Table 7.

Weekly differential blood counts including reticulocytes (calculate reticulocyte index, RI = Ret count x haematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct) and peripheral blood smear should be considered . If any blood parameters remain clinically abnormal after 28 days of dose interruption, the patient should be considered to be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

Development of myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the Investigator to AstraZeneca Patient Safety. All sudy treatment should be discontinued if a diagnosis of myelodysplastic syndrome is confirmed.

Management of new or worsening pulmonary symptoms:

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Study Physician.

5.5.3.1 Management of haematological toxicity (paclitaxel and olaparib)

At the first occurrence of CTCAE grade 3 and 4 haematological toxicity, both olaparib and paclitaxel should be held until resolution of toxicity. At the resolution of the first occurrence of any of these toxicities, no change should be made to dose. At the second occurrence, upon resolution of toxicity, olaparib should be reduced by the 1st dose reduction to 100 mg bd days 1-14 of a 28-day cycle (see Table 5). If despite this change, at the third occurrence, upon resolution of toxicity, paclitaxel should be reduced by the first dose reduction to 65 mg/m^2/dose (see Table 6). At the fourth occurrence, upon resolution of toxicity, olaparib should be reduced by the 2nd dose reduction to 100 mg bd days 1-7 of a 28-day cycle (see Table 5). If despite these changes, toxicity recurs, the patient should be withdrawn from the treatment.

Refer to Table 7 for specific dose modification guidance regarding haematological toxicity.

Please note that for simultaneous toxicities (for example, neutropenia and thrombocytopenia), if either olaparib or paclitaxel has been recently held or dose-reduced, and a second toxicity develops, the event should be considered singular and no further dose modification should be made, providing that both toxicities resolve within 28 days. However, sequential toxicities (for example, neutropenia followed by thrombocytopenia) should follow Table 7; if a recent dose reduction has been made, a second modification may be required before beginning the next cycle.

Table 5 Dose Reductions for Olaparib when Combined with Paclitaxel

Reduction	Dose Level
Initial Dose Level	100 mg bd days 1-28 of a 28-day cycle
1st dose reduction [a]	100 mg bd days 1-14 of a 28-day cycle
2nd dose reduction [a]	100 mg bd days 1-7 of a 28-day cycle
3rd Dose reduction	No reduction allowed; withdraw patient

a Dose must not be re-escalated even if toxicities have resolved.

Table 6 Dose Reductions for Paclitaxel

Reductions	Dose Level
Initial dose level	80 mg/m^2 on days 1, 8 and 15 of a 28-day cycle
1st dose reduction [a]	65 mg/m^2 on days 1, 8 and 15 of a 28-day cycle
2nd dose reduction	No additional reduction allowed; stop paclitaxel

[a] Dose may be re-escalated to full dose once toxicities have resolved, depending on toxicity (see below for exceptions).

Filgrastim or PEG-filgrastim may be used at the investigator's discretion.

In addition, paclitaxel should be permanently reduced to 65 mg/m^2/dose in case of the following haematological toxicities:

- Febrile neutropenia (temperature ≥ 38.5°C, ANC < 1.0 × 10^9/L), requiring hospitalisation and IV antibiotics.
- Bleeding associated with platelet count of ≤ 40 × 10^9/L or any platelet count of ≤ 20 × 10^9/L.

5.5.3.2 Management of non-haematological treatment-related adverse events attributable to olaparib

Non-hematological CTCAE grade 3 and 4 toxicities observed during the course of the study and attributable to olaparib will first be managed by interruption of the dose. Repeat dose interruptions are to be allowed as required. The maximum duration of any dose interruption is 28 days. If an interruption of longer than 28 days is required, the patient should be withdrawn. When olaparib is interrupted, the patient must either recover completely or the toxicity must revert to NCI CTCAE ≤ grade 1 or to the baseline CTCAE grade before restarting treatment. Patients whose NCI CTCAE grade 3 or 4 event does not resolve to ≤ grade 1 or to the baseline CTCAE grade after a full 28 day dose interruption should be withdrawn from the study.

Where toxicity recurs following re-challenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then dose reduction or withdrawal is indicated.

Upon appropriate resolution of the toxicity (i.e. to CTCAE grade 1 or to baseline CTCAE grade), the patient should restart treatment with olaparib but with a 50% dose reduction (as per Table 5).

If the event recurs with the same severity, treatment should be interrupted again and, on resolution, a further dose reduction made.

5.5.3.3 Management of non-haematologic treatment related adverse events attributable to paclitaxel

Treatment with paclitaxel may be continued on Day 1, 8, 15 of each cycle as long as each of the following criteria are met:

- AST ≤ 5 × ULN
- Bilirubin < 27 μmol/L (1.6 mg/dL)

If any of the following criteria are met:

- AST > 5 × ULN and ≤ 10 × ULN
- Bilirubin 27-43 μmol/L (1.6-2.5 mg/dL)

Then hold paclitaxel until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 65 mg/m^2. Dose may return to full dose (80 mg/m^2) in subsequent cycles. If paclitaxel is withheld for >1 cycle (28 days) the patient should not restart paclitaxel.

In the case of CTCAE grade 3 neuropathy, paclitaxel should be withheld and then resumed at 65 mg/m^2 on resolution to CTCAE grade 1 or less.

Paclitaxel should be permanently discontinued for the following non-haematological toxicities:

- Severe hypersensitivity reactions.
- CTCAE grade 3 or 4 neuropathy lasting more than 4 weeks.
- CTCAE grade 3 or 4 neuropathy recurring after dose reduction.
- AST and/or ALT CTCAE grade 3 or above (CTCAE grade 4 or above in case of liver metastases) lasting more than 7 days.
- Bilirubin CTCAE grade 3 or above.

Dose delays of paclitaxel as a consequence of non-haematological toxicities:

The treatment of a patient can be postponed for up to 28 days (one cycle) if the patient has not recovered to CTCAE grade 1 or less non-haematological toxicity at the beginning of cycle (Day 1).

Dose reductions of paclitaxel as a consequence of non-haematological toxicities:

For non-haematological toxicities other than those mentioned above and excluding nausea, vomiting and asthenia:

- If CTCAE grade 3, patients should have a permanent dose reduction to 65 mg/m^2
- Patients who experience CTCAE grade 4 non-haematological toxicity may have their dose held for up to 28 days (one cycle) to permit recovery to CTCAE grade 3 or below followed by a permanent dose reduction to 65 mg/m^2

Hypersensitivity reactions:

Discontinue paclitaxel infusion for significant hypersensitivity reactions defined as:

- Hypotension requiring pressor therapy.
- Angioedema.
- Respiratory distress requiring bronchodilator therapy.
- Generalised urticaria.

For other hypersensitivity reactions, paclitaxel may be discontinued at the discretion of the investigator.

Any significant hypersensitivity reaction and any hypersensitivity reaction requiring treatment discontinuation should be reported as an AE or SAE.

The following management of hypersensitivity reactions is recommended or local standard practice:

- Administer chlorpheniramine 10 mg IV, or equivalent.
- Administer adrenaline (or its equivalent) sub-cutaneous every 15-20 minutes until the reaction subsides or a total of 6 doses given.
- If hypotension is present that does not respond to adrenaline, administer IV fluids.
- If wheezing is present that is not responsive to adrenaline, administration of nebulized salbutamol solution (or equivalent) is recommended.

Although corticosteroids have no effect on the initial reaction, they have been shown to block "late" allergic reactions to a variety of substances. Thus, methylprednisolone 125 mg IV (or its equivalent) may be administered to prevent recurrent or ongoing allergy manifestations.

Patients should not be re-challenged with paclitaxel in case of a severe hypersensitivity reaction. These patients should be discontinued from treatment with paclitaxel.

Table 7 Summary of Guidance on the Management of Toxicity for Olaparib and Paclitaxel

Toxicity	Olaparib	Paclitaxel
Haematological toxicities		
Neutropenia ANC > 1×10^9/L and < 1.5 $\times 10^9$/L (CTCAE grade 2)	No action required.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at original dose. If withheld for > 28 days patient should not restart paclitaxel.
Neutropenia ANC ≤ 1×10^9/L (CTCAE grade ⩾ 3)	1st occurrence Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at original dose level. If symptoms do not recover to ≤ CTCAE grade 1, discontinue olaparib.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at original dose. If withheld for > 28 days patient should not restart paclitaxel.
	2nd occurrence Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at 1st reduced dose level. If symptoms do not recover to ≤ CTCAE grade 1, discontinue olaparib.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at original dose. If withheld for > 28 days patient should not restart paclitaxel.

Table 7 Summary of Guidance on the Management of Toxicity for Olaparib and Paclitaxel

Toxicity	Olaparib	Paclitaxel
	3rd occurrence Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at 1st reduced dose level. If symptoms do not recover to ≤CTCAE grade 1, discontinue olaparib.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at reduced dose of 65 mg/m^2. If withheld for >28 days patient should not restart paclitaxel.
	4th occurrence Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at 2nd reduced dose level. If symptoms do not recover to ≤CTCAE grade 1, discontinue olaparib.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at a dose of 65 mg/m^2. If withheld for >28 days patient should not restart paclitaxel.
Febrile neutropenia (temperature ≥ 38.5°C, ANC < 1.0 × 10^9/L), requiring hospitalisation and IV antibiotics	Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at original dose level. If symptoms do not recover to ≤ CTCAE grade 1, discontinue olaparib.	Permanent dose reduction to 65 mg/m^2.
Bleeding associated with platelet count of ≤ 40 × 10^9/L or any platelet count of ≤ 20 × 10^9/L (CTCAE grade ⩾3)	Withhold dose for up to 28 days until recovery to ≤CTCAE grade 1 then resume at original dose level. If symptoms do not recover to ≤CTCAE grade 1, discontinue olaparib.	Permanent dose reduction to 65 mg/m^2.
Platelets > 20 × 10^9/L and < 100 x10^9/L	No action required.	Reduce dose to 65 mg/m^2, may be re-escalated at next cycle.
Peripheral neuropathy		
CTCAE grade 2	No change	Start next course with dose reduced by 1 dose level (65 mg/m^2)

Table 7 Summary of Guidance on the Management of Toxicity for Olaparib and Paclitaxel

Toxicity	Olaparib	Paclitaxel
CTCAE grade 3	Withhold dose for up to 1 cycle (28 days) until recovery to ≤CTCAE grade 1 then dose reduce by 1 dose level. If symptoms do not recover, discontinue olaparib	Withhold paclitaxel for minimum of 1 cycle (28 days) until recovery to ≤CTCAE grade 1 then dose reduce subsequent cycles to 65 mg/m^2. If symptoms recur after dose reduction discontinue paclitaxel
Hepatotoxicity	For CTCAE grade ≥ 3 rises in AST/ALT or bilirubin: Withhold dose for up to 1 cycle (28 days) until recovery to ≤ CTCAE grade 1 then dose reduce by 1 dose level. If symptoms do not recover to ≤ CTCAE grade 1, discontinue olaparib	If AST or ALT > 5 × ULN and ≤ 10 × ULN or Bilirubin 27-43 µmol/L 1.6 – 2.5 mg/dL then: • Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 65 mg/m^2. Dose may return to full dose (80 mg/m^2) in subsequent cycles. If withheld for > 1 cycle (28 days) patient should not restart paclitaxel In case of AST and/or ALT CTCAE grade 3 or above (CTCAE grade 4 in case of liver metastases) lasting more than 7 days Or Bilirubin CTCAE grade 3 or above then: • Stop paclitaxel
Other non-haematological toxicities (excludes nausea, vomiting, asthenia) that are not listed above		
CTCAE grade 3	Withhold dose for up to 1 cycle (28 days) until recovery to ≤ CTCAE grade 1, reduce by 1 dose level	Permanent dose reduction to 65 mg/m^2
CTCAE grade 4	Withhold dose for up to 1 cycle (28 days) until recovery to ≤ CTCAE grade 1, reduce by 1 dose level	Withhold dose for up to 1 cycle (28 days) until recovery to CTCAE grade 3 or below, permanent dose reduction to 65 mg/m^2
CTCAE grade 3 or 4 allergic reaction/hypersensitivity that is clearly attributable to paclitaxel	No change	Stop paclitaxel

5.5.4 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Specific dosing instructions will not be included on the label, the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing.

The patient emergency contact details will not be on the label, but can be found in the informed consent and the "Patient Dispensing Card". For emergency purposes the patient must be in possession of the emergency contact details at all times.

5.5.5 Storage

All study drugs must be kept in a secure place under appropriate storage conditions and may only be dispensed by a pharmacist or a qualified designee. The investigational product label on the bottle specifies the appropriate storage.

5.6 Concomitant and post-study treatment(s)

No other chemotherapy, immunotherapy, or other novel agent is to be permitted while the patient is receiving study treatment.

Other medication, which is considered necessary for the patient's safety and well being during the treatment period of Part B, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

5.6.1 Olaparib and drug-drug interaction

The use of any natural/herbal products or other "folk remedies" should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded eCRF

Effect of Other Drugs on Olaparib

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. Clinical studies to evaluate the impact of known CYP3A inhibitors and inducers have shown that co-administration of a potent CYP3A inhibitor increased olaparib Cmax 1.42-fold (90% CI: 1.33-1.52) and increased mean AUC 2.70-fold (90% CI: 2.44-2.97) and that co-administration of a potent CYP inducer decreased Cmax by 71% (Treatment ratio: 0.29; 90% CI: 0.24-0.33) and mean AUC by 87% (Treatment ratio: 0.13; 90% CI: 0.11-0.16). It is therefore recommended that known strong inhibitors or inducers of these isozymes should be avoided with olaparib.

While this is not an exhaustive list, it covers the known potent CYP3A4/5 inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, boosted protease inhibitors (indinavir, saquinavir, telithromycin, and nelfinavir, boceprevir, telaprevir) and clarithromycin

For patients taking any of the above, the required wash-out periods prior to starting study treatment is one week.

In addition, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4/5 inducers should be avoided:

- Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St John's Wort (Hypericum perforatum)

For patients taking any of the above CYP3A4/5 inducers, the required wash-out periods prior to starting study treatment in part A are :

- phenobarbitone 5 weeks, and
- for any of the others, 3 weeks.

After completing the treatment period of Part A, if the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the investigator must contact the AstraZeneca Study Physician. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

Long term use of potent inducers and inhibitors of CYP3A4/5 should be avoided. If a decision is made to allow patients to use a potent inducer or inhibitor then they must be monitored carefully for any change in efficacy or safety of olaparib.

In vitro olaparib is a substrate for the efflux transporter Pgp. Clinical studies to evaluate the impact of known Pgp inhibitors and inducers have not been conducted.

Effect of Olaparib on Other Drugs

Olaparib can inhibit CYP3A4 and UGT1A1 *in vitro*. These findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 substrates or UGT1A1 substrates in the liver or gastrointestinal tract. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (eg, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (eg, irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine).

Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro with CYP3A4 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and Pgp is unknown. It cannot be excluded that olaparib upon co administration may reduce the exposure to substrates of these metabolic enzymes and

transport protein. The efficacy of hormonal contraceptives may be reduced if co administered with olaparib.

In vitro olaparib has been shown to be an inhibitor of Pgp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K and is a weak inhibitor of BRCP. It cannot be excluded that olaparib may increase the exposure to substrates of P gp (eg, statins, digoxin, dabigatran, colchicine), OATP1B1 (eg, bosentan, glibenclamide, repaglinide, statins, and valsartan), OCT1 (eg, metformin), OCT2 (eg, serum creatinine), OAT3, MATE1 and MATE2K. In particular, caution should be exercised if olaparib is administered in combination with any statin.

5.6.2 Anticoagulant Therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (international normalised ratio (INR) and activated partial thromboplastin time (APTT)) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

5.6.3 Anti-emetics/Anti-diarrhoeals

Should a patient develop nausea, vomiting and or diarrhoea, then these symptoms should be reported as AEs (see section 6.3) and appropriate treatment of the event given.

5.6.4 Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

5.7 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

Investigational site personnel will administer study medication for patients in the single dose period and the in-house days of multiple dose period; the oral cavity of each subject will be examined following dosing to assure the study medication was taken.

Patients will self-administer olaparib during outpatient periods; they should be given clear instructions on how and when to take their study treatment. Compliance of the first dose and dose taken on the day of any study visit of olaparib will be assured by supervised administration by the investigator or delegate.

Subjects will be required to record each daily dose in a dosing diary throughout the Part A period, and the compliance will be assessed at each visit by site investigator(s) by review of the diary as well as returned medication; during Part B period, the compliance will be assessed at specific visits (see Table 1 and Table 2) by site personnel by review of returned medication.

Compliance will be calculated at each visit by the site staff according to the following equation during the Part A period:

Percent compliance = (number of tablets taken/number of tablets expected to be taken) x 100

In Part A period, the Percentage of compliance should be 100%, any subject who is considered non-compliant must be discussed with Astrazeneca study team members and considered for possible withdrawal from the study.

All returned containers (empty and not empty) of study medication will be kept available for possible review by the study monitor.

After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the Investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded on the eCRF.

5.7.1 Accountability

The study drug provided for this study is for use only as directed in the study protocol. It is the investigator/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, so as to ensure that:

- Deliveries of such products from AstraZeneca are correctly received by a responsible person
- Such deliveries are recorded
- Study treatments are handled and stored safely and properly as stated on the label
- Study treatments are only dispensed to study patients in accordance with the protocol

The study personnel will account for all study medications dispensed and returned. Certificates of delivery and return should be signed.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed, the quantity and date of dispensing and unused study treatment returned to the investigator. This record is in addition to any drug

accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist, and copies retained in the investigator site file.

5.8 Discontinuation of investigational product

Subjects may be discontinued from investigational product (IP) in the following situations:

Patients may be discontinued from investigational product in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance to study protocol
- Disease progression (unless in the investigator's opinion they are clinically benefiting from continuing treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8)
- Pregnancy

5.8.1 Procedures for discontinuation of a subject from investigational product

A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Section 6.3.3and Section 6.3.4); and all study drugs should be returned by the subject.

If a subject is withdrawn from study, see Section 5.9.

Any patient discontinuing investigational product should be seen at 30 days post-discontinuation for the evaluations outlined in the study schedule.

After discontinuation of the study medication at any point in the study, all ongoing AEs and SAEs must be followed until resolution unless, in the investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see Sections 6.3.3and Section 6.3.4). All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 6.3.4) and followed to resolution as above. Patients should be contacted at least 30 days after discontinuing study medication to collect and /or complete AE information. Any untoward event occurring subsequent to the 30 days follow-up AE reporting period that the investigator assesses as possibly related to the study medication should also be reported as an AE.

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible they will be seen and assessed by an investigator. Adverse events will be followed up (see Section 6.3.3 and Section 6.3.4) and all study drugs should be returned by the patient.

Withdrawn patients will not be replaced.

Reasons for withdrawal from the study:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment
- Severe non-compliance to protocol as judged by the Investigator and/or AstraZeneca
- Incorrectly enrolled patients i.e. the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- Adverse event
- Death
- Disease progression
- Pregnancy

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

6.2 Data collection at enrolment and follow-up

6.2.1 Screening procedures

The following assessments and procedures should be performed within 28 days prior to first dose of study treatment to confirm that the patients meet the study selection criteria.

The following procedures will be completed.

- Obtain written Informed Consent before performing any study related activities.
- Date of birth, race and ethnicity
- Medical and surgical history
- Current and concomitant medications including previous cancer therapies
- Record Primary Diagnosis
- Physical examination
- ECOG performance status
- Vital signs (supine blood pressure, pulse and body temperature), body weight and height.
- Following at least a 4-hour fast, blood and urine specimens will be collected for the following:
  - Safety laboratory tests: Haematology, clinical chemistry and urinalysis
  - Hepatitis B surface antigen, anti HCV IgG test, HIV test;
  - Serum/urine pregnancy test for females of childbearing potential(which should be repeated for eligible patients on Day 1 of Part A prior to study treatment);
  - Serum LH and FSH concentrations in all female subjects of non-childbearing potential who are under 50 years of age; to confirm post-menopausal status to confirm eligibility with regards to non-child bearing potential
- Adverse events must be captured from time of consent
- Perform a 12-lead ECG.
- Estimate Creatinine clearance, which should > 50 mL/min calculated by Cockcroft-Gault equation.

$$\text{Males: } CL_{CR} = \frac{(140\text{-age}) \times (\text{kg body weight})}{(72 \times \text{mg/dl serum creatinine})}$$

$$\text{Females: } CL_{CR} = \frac{(140\text{-age}) \times (\text{kg body weight}) \times 0.85}{(72 \times \text{mg/dl serum creatinine})}$$

The Principal investigator/sub-investigator should adhere to the study plan, procedures and perform tests/observations in accordance with the protocol.

6.2.2 Treatment procedures

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- ECG recordings
- Vital signs: obtain as close as possible to scheduled time, but prior to blood specimen collection.
- Pharmacokinetic blood specimens: obtain at scheduled time.
  Blood sampling for laboratory assessments
- Other procedures: obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection

The actual time for all assessments will be recorded in the eCRF. Pre-dose assessments, may be done up to 60 minutes prior to dosing.

For eligible patients, during Part A treatment, they may be required to stay in house for intensive PK sampling and then as outpatient for required PK sample draws. The recommended schedule is as following:

- For Cohort 1, patients may be admitted to the CPU on Day -1(or in the morning of Day 1 dependent on the site's administration), and will remain in-house up to the collection of the 24 hour pharmacokinetic sample on Day 2; the 48 hour PK sample on Day 3 can be collected as outpatient; the patients may be required to return to study site on multiple dose period Day 7(or in the morning of Day 8 dependent on the site's administration), and stay in the site until the last pharmacokinetic sample for Day 8 is drawn.
- For Cohort 2, patients may be admitted to the CPU on Day -1(or in the morning of Day 1 dependent on the site's administration), and will remain in-house up to the collection of the 24 hour pharmacokinetic sample on Day 2; the 48 hour PK sample

on Day 3 can be collected as outpatient; the patients may be required to return to study site on multiple dose period Day 7(or in the morning of Day 8 dependent on the site's administration), and stay in the site until the last pharmacokinetic sample for Day 9 is drawn.

PK sample collection time points, refer to Table 1, and Table 2, as well as Section 6.4 for details. On the intensive PK sampling days, prior to dosing, the site personnel will insert intravenous catheter for collection of blood samples as deemed necessary.

Investigational site personnel will administer study medication for patients in the single dose period and the in-house days of multiple dose period; Patients will self-administer olaparib during outpatient periods; they should be given clear instructions on how and when to take their study treatment. Compliance of the first dose and dose taken on the day of any study visit of olaparib will be assured by investigational site personnel.

For patients on Cohort 1, after the completion of PK sampling phase in Part A (single dose period, and Days 1-8 of multiple dose period), during the Part B multiple dose treatment period, they will visit the study site on Days 1 (1st day of Part B treatment), 8, 15, 22, 29, and every 28 days thereafter and the following assessments will be performed at time points specified in the study schedule (see Table 1).

- Vital signs
- Physical examination including ECOG performance status (Day 1 of each 4 week period)
- ECG (Day 1 of each 4 weeks period)
- Haematology, clinical chemistry and urinalysis
- AE, include Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Review concomitant medications
- Review concomitant non drug treatment procedures

For patients on Cohort 2, after the completion of PK sampling phase in Part A(single dose monotherapy period and multiple dose multiple dose monotherapy period), during the multiple dose combination period of Part A and multiple dose combination period of Part B, they will visit the study site on Days 9 (Cycle 1 Day 1 of paclitaxel treatment),16, 23, 30, and weekly paclitaxel treatment days (e.g. Days 37, 44, 51, 58 in Cycle 2)thereafter from Cycle 2 to Cycle 9, the following assessments will be performed at time points specified in the study schedule (see Table 2)

- Vital signs
- Physical examination including ECOG performance status (Day 1 of each 4 week period)
- ECG (Day 1 of each 4 weeks period)
- Haematology, clinical chemistry and urinalysis
- AE, include Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Review concomitant medications
- Review concomitant non drug treatment procedures

In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.

6.2.3 Treatment discontinuation visit

Patients should be discontinued from study treatment if any discontinuation criteria are fulfilled (see Section 5.8). The assessments to be carried out at the visit are detailed in the study schedule (see Table 1 and Table 2).

6.2.4 Follow-up procedures (30 days after last dose of study medication)

Follow up visit should be conducted 30 days after the last dose of olaparib. Any serious and/or non-serious AEs ongoing at the time of the Discontinuation Visit or which have occurred during the defined 30-day follow up period must be followed-up (in accordance with Sections 6.3.3and 6.3.4). Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the eCRF.

6.3 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.3.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the

abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.3.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.3.3 Recording of adverse events

Time period for collection of adverse events

AEs will be collected from time of signature of informed consent, throughout the treatment period and up to and including the 30 days follow-up period. All ongoing and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution. After any interim analysis, any ongoing AEs/SAEs need to be unlocked and followed for resolution.

SAEs will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

Any SAE or non-serious AE that is ongoing at the time of the 30 days follow-up, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Post Follow-up adverse events

After study treatment completion (i.e. after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (30 days). If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AstraZeneca, Patient Safety.

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and / or post study completion then as a minimum all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe (Section 6.3.4).

Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study *(*yes or no*)*
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE.

Severity of AE

For each episode on an AE, all changes to the CTCAE grade attained as well as the highest attained CTCAE grade should be reported.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

The grading scales found in the National Cancer Institute (NCI) CTCAE version 4.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades the recommendation is that the CTCAE criteria that convert mild, moderate and severe events into CTCAE grades should be used.

A copy of the CTCAE version 4.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes’.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: ‘Have you had any health problems since the previous visit/you were last asked?’, or revealed by observation will be collected and recorded in the CRF. When

collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

NB. Cases where a subject shows an AST **or** ALT ≥3×ULN **or** total bilirubin ≥ 2×ULN may need to be reported as SAEs, please refer to Appendix F 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the signs and symptoms of the cancer. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

New cancers

The development of a new primary cancer (including skin cancer) should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 6.3.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

Lack of efficacy

When there is deterioration in the patient's primary diagnosed cancer, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the DEATH eCRF but should not be reported as an SAE

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 6.3.4 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.

Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca within the usual timeframes.

6.3.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (see Table 1 and Table 2).

The lab safety assessments may not need to be repeated on Day 1 of Part A if these tests are performed on Days -2 or Day -1 during Screening.

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

The following laboratory variables will be measured:

Table 8 Laboratory Tests

Clinical chemistry	**Haematology**
Urea / BUN	Haemoglobin
Creatinine	Erythrocyte count
Glucose	Haematocrit
Sodium	Platelet count
Potassium	Total Leucocyte count
Calcium	Mean cell haemoglobin concentration (MCHC)
Albumin	Mean cell volume (MCV)
Total bilirubin	Mean cell haemoglobin (MCH)
Alkaline phosphatase (ALP)	Monocytes
Asparate aminotransferase (AST)	Eosinophils
Alanine aminotransferase (ALT)	Basophils

Table 8 Laboratory Tests

Clinical chemistry	**Haematology**
Gamma glutamyltransferase (GGT)	Neutrophils
Total protein	Lymphocytes
Conjugated bilirubin (if total bilirubin elevated)	
Chloride	**Serology**
	HIV
Urinalysis	Hepatitis B surface antigen;
Glucose	Anti HCV IgG
Protein	
Blood	**Others**
	hCG[a]
	FSH[b]
	LH[b]

a. Serum/urine pregnancy test is required for females of childbearing potential;
b. Serum LH and FSH concentrations are required for female subjects of non-childbearing potential who are under 50 years of age; to confirm post-menopausal status to confirm eligibility with regards to non-child bearing potential.

NB. In case a subject shows an AST **or** ALT ≥3×ULN **or** total bilirubin ≥ 2×ULN please refer to Appendix F 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

For blood volume see Section 7.1.

6.3.6 Physical examination

For timing of individual measurements refer to the Study Schedule (see Table 1and Table 2).

A complete physical examinations will be performed including an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.

Performance status will be assessed using the ECOG scale (see Appendix G) at screening and as outlined in the study schedule. The same observer should assess performance status each time.

If being assessed within 7 days before first dosing of study medication and meets the stated eligibility criteria (if applicable), it may not be repeated on Day 1 of Part A, unless investigator believes that it is likely to have changed significantly.

6.3.7 ECG

6.3.7.1 Resting 12-lead ECG

For timing of individual measurements refer to study plan (see Table 1 and Table 2).

If being assessed within 7 days before first dosing of study medication and meets the stated eligibility criteria (if applicable), it may not be repeated on Day 1 of Part A, unless investigator believes that it is likely to have changed significantly.

12-lead ECGs will be obtained after the patient has been lying down for 10 minutes in each case. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF.

6.3.8 Vital signs

6.3.8.1 Pulse and blood pressure

For timing of individual measurements refer to study plan (see Table 1 and Table 2).

Supine BP and HR will be measured in accordance with normal clinical practice and recorded to the nearest mm Hg after patients have been lying supine for 5 minutes. The same arm (preferably the dominant arm) will be used throughout the study.

6.3.8.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in the Study Plan and Time Schedule (see Table 1 and Table 2).

6.4 Pharmacokinetics

6.4.1 Collection of samples

Blood samples (4.0 mL) for determination of olaparib in plasma will be taken at the times presented in the study plan (see Table 1 and Table 2).

For Cohort 1, during single dose period, PK samples will be collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 (Day 2) and 48 h (Day 3); during the multiple dose period, PK samples will be collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h post morning dose of Day 8.

For Cohort 2, during single dose period, PK samples will be collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 (Day 2) and 48 h (Day 3); during the multiple dose monotherapy period, PK samples will be collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6,8 and 12 h post morning dose of Day 8, and pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6,8 and 12 h post

morning dose of Day 9 (Multiple dose combination period, Cycle 1 Day 1 of paclitaxel treatment)

The actual times of every sample drawn may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, eCRF).

Individual venipunctures for each time point may be performed or an indwelling catheter may be used.

Samples for the measurement of concentration should be analysed within the timeframe after collection for which the stability in the samples has been validated and found acceptable. Results from analyses stored longer than the period stated will not be reported.

Samples will be collected, labelled stored and shipped as detailed in Laboratory Manual.

Table 9 Schedule of Olaparib Pharmacokinetic Blood Sampling for Measurement of Drug Concentration-Cohort 1

Study visit	Analyte	Scheduled time relative to olaparib dose (h)	Tube number
Visit 2/Day1(single dose period)	olaparib	Pre-dose	1
	olaparib	0.25 hr	2
	olaparib	0.5 hr	3
	olaparib	1 hr	4
	olaparib	1.5 hr	5
	olaparib	2 hr	6
	olaparib	3 hr	7
	olaparib	4 hr	8
	olaparib	6 hr	9
	olaparib	8 hr	10
	olaparib	12 hr	11
Visit 2/Day 2 (single dose period)	olaparib	24 hr	12
Visit 3/ Day 3 (single dose period)	olaparib	48 hr	13
Visit 5/Day 8(Multiple dose period)	olaparib	Pre-dose	14

Table 9 Schedule of Olaparib Pharmacokinetic Blood Sampling for Measurement of Drug Concentration-Cohort 1

Study visit	Analyte	Scheduled time relative to olaparib dose (h)	Tube number
	olaparib	0.25 hr	15
	olaparib	0.5 hr	16
	olaparib	1 hr	17
	olaparib	1.5 hr	18
	olaparib	2 hr	19
	olaparib	3 hr	20
	olaparib	4 hr	21
	olaparib	6 hr	22
	olaparib	8 hr	23
	olaparib	12 hr	24

Table 10 Schedule of Olaparib Pharmacokinetic Blood Sampling for Measurement of Drug Concentration-Cohort 2

Study visit	Analyte	Scheduled time relative to olaparib dose (h)	Tube number
Visit 2/Day1 (single dose monotherapy period)	olaparib	Pre-dose	1
	olaparib	0.25 hr	2
	olaparib	0.5 hr	3
	olaparib	1 hr	4
	olaparib	1.5 hr	5
	olaparib	2 hr	6
	olaparib	3 hr	7
	olaparib	4 hr	8
	olaparib	6 hr	9
	olaparib	8 hr	10
	olaparib	12 hr	11
Visit 2/Day 2 (single dose monotherapy period)	olaparib	24 hr	12
Visit 3/ Day 3 (single dose monotherapy period)	olaparib	48 hr	13

Table 10 Schedule of Olaparib Pharmacokinetic Blood Sampling for Measurement of Drug Concentration-Cohort 2

Study visit	Analyte	Scheduled time relative to olaparib dose (h)	Tube number
Visit 5/Day 8 (Multiple dose monotherapy period)	olaparib	Pre-dose	14
	olaparib	0.25 hr	15
	olaparib	0.5 hr	16
	olaparib	1 hr	17
	olaparib	1.5 hr	18
	olaparib	2 hr	19
	olaparib	3 hr	20
	olaparib	4 hr	21
	olaparib	6 hr	22
	olaparib	8 hr	23
	olaparib	12 hr	24
Visit 6/Day 9 (Multiple dose combination period)	olaparib	Pre-dose	25
	olaparib	0.25 hr	26
	olaparib	0.5 hr	27
	olaparib	1 hr	28
	olaparib	1.5 hr	29
	olaparib	2 hr	30
	olaparib	3 hr	31
	olaparib	4 hr	32
	olaparib	6 hr	33
	olaparib	8 hr	34
	olaparib	12 hr	35

For blood volume see Section 7.1.

6.4.2 Determination of drug concentration

Samples for determination of olaparib concentrations in plasma will be analyzed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate

bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 11 Volume of Blood to be Drawn from Each Subject-Cohort 1

Assessment		Sample volume [a] (mL)	No. of samples[b]	Total volume (mL)
Safety	Clinical chemistry	5	15	75
	Haematology	2	15	30
Serology[c]		10	1	10
Pharmacokinetics		4	24	96
Discard sample prior to PK sample[d]		2	24	48
Serum β-HCG[e]		4	2	8
Total				267[f]

a The sample volume for safety assessments, Serology, serum β-HCG are approximate volumes that are patient to site-specific change.
b Number of samples is estimated based on patients on average completing 6 cycles in Part B therapy.
c The Serology test includes: Hepatitis B surface antigen; Anti HCV IgG; HIV
d This discarded blood from predraws used to remove fluid from flushed catheters, the discarded volume is not expected to exceed 2 mL for each PK draw point.
e Only for women of childbearing potential
f For women under age 50 who reported post menopausal, an additional 6 mL of blood will be taken to perform a serum LH and FSH levels tests at the Screening visit. This total volume does not include these tests.

Table 12 Volume of Blood to be Drawn from Each Subject-Cohort 2

Assessment		Sample volume [a] (mL)	No. of samples[b]	Total volume (mL)
Safety	Clinical chemistry	5	29	145
	Haematology	2	29	58
Serology[c]		10	1	10
Pharmacokinetics		4	35	140
Discard sample prior to PK sample[d]		2	35	70
Serum β-HCG[e]		4	2	8

Table 12 Volume of Blood to be Drawn from Each Subject-Cohort 2

Assessment	Sample volume [a] (mL)	No. of samples[b]	Total volume (mL)
Total			431[f]

a. The sample volume for safety assessments, Serology, serum β-HCG are approximate volumes that are patient to site-specific change.
b. Number of samples is estimated based on patients on average completing 6 cycles in Part B therapy.
c. The Serology test includes: Hepatitis B surface antigen; Anti HCV IgG; HIV
d. This discarded blood from predraws used to remove fluid from flushed catheters, the discarded volume is not expected to exceed 2 mL for each PK draw point.
e. Only for women of childbearing potential
f. For women under age 50 who reported post menopausal, an additional 6 mL of blood will be taken to perform a serum LH and FSH levels tests at the Screening visit. This total volume does not include these tests.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses and the clinical study report has been finalized.

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR. Anonymised samples will be retained for no more than 5 years after the CSR is finalised.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Report.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first subject is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate subjects for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

9.2 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)

- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

Refer to the Clinical Study Agreement for location of source data

9.4 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study', this may be due to all the patients having progressed disease/withdraw from the study, or is 12 months after LSI. At this time point, the clinical study database will close to new data. Patients are, however, permitted to continue to receive olaparib beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from treatment with olaparib. For patients who do continue to receive treatment beyond the closure of the database, investigators will continue to report all SAEs to AstraZeneca Patient Safety

until 30 days after IP is discontinued, in accordance with Section 6.3.4 (Reporting of serious adverse events). Additionally, as stated in Section 6.3.3 (Recording of adverse events), any SAE or non-serious AE that is ongoing at the time defined as the end of the study must be followed up to resolution unless the event is considered by the Investigator to be unlikely to resolve, or the patient is lost to follow-up.

The study is expected to start in Q2 2015 and to end by Q1 2017.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with olaparib.

10. DATA MANAGEMENT BY ASTRAZENECA

Data management will be performed by Cognizant.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the Data Management Centre.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR ITS REPRESENTATIVE

11.1 Calculation or derivation of safety variable(s)

Where appropriate, change-from-baseline variables will be calculated for the continuous variables as the post-treatment value minus the value at baseline.

Baseline for Haematology and Clinical Chemistry will be defined as the value measured Day-1. If a patient is missing the baseline collection, the previous nonmissing evaluation will become the baseline value. If no baseline or previous-to-baseline evaluation exists then the baseline value will be treated as missing.

Adverse Events will be classified by type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] Version 4.0), timing, seriousness, and relatedness.

11.1.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations of IP due to AEs (DAEs). Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

11.2 Calculation or derivation of pharmacokinetic variables

The PK analyses of the plasma concentration data for olaparib will be done at AstraZeneca R&D. The actual sampling times will be used in the PK calculations. PK parameters will be determined using standard non-compartmental methods.

Patients who withdraw from the study following dosing, but prior to study completion, will be included in the PK analysis provided they have evaluable profiles over the planned collection period. Patients with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for meaningful analysis.

If sufficient data are available for estimation, the following single-dose PK parameters will be calculated for olaparib 300 mg and olaparib 100 mg monotherapy in Part A:

- Maximum plasma concentration (C_{max}) obtained directly from the observed concentration-versus-time data
- Time to maximum plasma concentration (t_{max}) obtained directly from the observed concentration-versus-time data
- Area under the plasma concentration-time curve from zero to 12 hours after dosing ($AUC_{[0-12]}$) calculated by linear up/log down trapezoidal summation

- Terminal rate constant (kel) estimated by log-linear least squares regression of the terminal part of the concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile.

- Area under the plasma concentration-time curve from zero (pre-dose) extrapolated to infinity (AUC) calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the terminal rate constant: $AUC_{(0-t)}+C_{last}/kel$.

- Terminal half-life ($t_{1/2}$) calculated from the terminal rate constant (terminal half life = ln 2/kel)

- Apparent plasma clearance (CL/F) calculated from dose/AUC

- Apparent volume of distribution (V_{ss}/F) calculated from CL/F × MRT

- Mean residence time (MRT)

- Temporal change parameter (TCP) at steady state calculated by AUCss (multiple dose)/AUC extrapolated to infinity (following a single dose)

If sufficient data are available for estimation, the following multiple dose PK parameters will be calculated for olaparib 300 mg monotherapy, olaparib 100 mg monotherapy and olaparib 100 mg in combination with paclitaxel in Part A:

- Maximum plasma concentration for steady state ($C_{max, ss}$) obtained directly from the observed concentration-versus-time data

- Minimum plasma concentration for steady state ($C_{min, ss}$) obtained directly from the observed concentration-versus-time data

- Time to maximum plasma concentration for steady state ($t_{max, ss}$) obtained directly from the observed concentration-versus-time data

- Area under the plasma concentration-time curve from zero (pre-dose) to 12 hours after dosing (AUC_{ss}) calculated by linear up/log down trapezoidal summation

- Apparent plasma clearance for steady state (CL_{ss}/F) calculated from dose/AUC_{ss}

- Accumulation index (RAC) calculated from $AUC_{ss}/AUC_{(0-12)}$ – monotherapy only

- DF calculated from $C_{max, ss}/C_{min, ss}$ – monotherapy only

If sufficient data are available for estimation, the following PK parameters of each analyte will be calculated for diagnostic purposes and listed but not summarised for plasma data:

- The time interval (λz upper and lower) of the log-linear regression to determine λz
- Number of data points (λz, N) included in the log-linear regression analysis to determine λz. A minimum of 3 data points will be used
- Coefficient of determination for calculation of λz (Rsq). If Rsq is 0.80 or less, λz and related parameters will not be reported
- The percent of AUC which is extrapolated to infinity (%AUCex). If the extrapolated area (Clast/λz) is greater than 20% of AUC, then AUC and related parameters will be not reported

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

12.1 Description of analysis sets

Table 13 Definition of Analysis Sets

Set	Population
PK analysis set	All patients who receive an olaparib dose and provide evaluable PK profiles in at least 1 treatment period.
Safety analysis set	All patients who receive at least 1 dose of olaparib

The study physician, pharmacokineticist, and statistician will agree the strategy for dealing with data affected by protocol deviations before any formal statistical analysis is performed.

If a patient has a major protocol deviation that affects the evaluability of the PK profile in either part of the study, then the patient will not form part of the PK analysis set for that part.

Major protocol deviations include changes to the procedures that may impact the quality of the data or any circumstances that can alter the evaluation of the PK. Examples include, but may not be limited to, vomiting following oral dosing occurring within the timeframe of 2 times the median t_{max}, sample processing errors that lead to inaccurate bioanalytical results, incomplete dose administered, incomplete PK profile collected, and/or use of disallowed concomitant medication. In the case of a major protocol deviation, affected PK data collected will be excluded from the summaries and statistical analyses, but will still be reported in the study result listings. Major deviations will be listed and summarised in the CSR.

12.2 Methods of statistical analyses

The following text applies to demographic and safety analyses only; PK is discussed separately.

Statistical analyses will be performed by the Biostatistics Group using SAS® v8.1 or higher and, where appropriate, additional validated software.

A comprehensive Statistical Analysis Plan (SAP) will be prepared by the biostatistician before database lock. For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarised using descriptive statistics, including n, mean, SD, median, minimum, and maximum values. Where appropriate, assessments will be summarised by visit.

The number of patients screened and included in the safety analysis set will be summarised. Demographic and baseline characteristics will be summarised and listed for the safety analysis set.

Treatment duration will be summarised. Treatment duration is based on the dates of first and last dose.

Study day will be calculated as follows:

Days prior to first dose: Study day=date – first dose date.

Days on or after first dose: Study day=date – first dose date+1.

No imputations will be made for any missing data.

12.2.1 Database locks and data analyses

After the last patient has completed the treatment period in Part A, the database for Part A of the study will be locked, the PRIMA analysis will be performed and the part A data will be reported in a CSR. The end of Part B will be date of the earliest of the following events:

- 12 months after last subject in
- All patients have terminated from study in both cohorts
  - For Cohort 1, patients terminate from study when they discontinue olaparib, which can be taken until the investigator feels the patient is no longer benefiting from treatment
  - For Cohort 2, patients terminate from study when they have received 6-9 cycles of chemotherapy in combination with olaparib

At the end of Part B the final analysis containing subsequent safety assessments will be performed and will be presented in a CSR addendum.

12.2.2 Pharmacokinetics

The sample bioanalysis will be performed by Covance. The merging of PK concentration data with actual PK sampling times will be performed by Data Management Centre. The PK analysis will be the responsibility of the pharmacokineticist at AstraZeneca. The PK

summaries, figures, and data listings as well as the statistical analysis of the PK variables will be the responsibility of the biostatistician.

All data received will be presented in data listings. Pharmacokinetic summaries will be presented for patients in the PK analysis set, as defined in Section 12.1. Data from patients excluded from the PK analysis set will be included in the data listings, but not in the summaries. Extra measurements (such as unscheduled or repeat assessments) will also not be included in summary tables, but will be included in patient listings.

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarised using descriptive statistics, including n, arithmetic mean, SD, coefficient of variation (%CV), median, minimum, and maximum values. Additionally, geometric means and geometric %CV (%GCV) will be reported for PK variables (concentrations and all PK parameters, except for t_{max}). The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The %GCV is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a log scale. Mean, SD, CV%, geometric mean, and %GCV will not be calculated for t_{max}; t_{max} will be summarised by median and range.

For all data, descriptive statistics except for %CV and %GCV will follow the rounding convention of the individual data. Coefficients of variation (%CV and %GCV) will always be reported to 1 decimal place.

The PK concentrations will be reported to the same precision as the source data. For descriptive statistics of concentrations, non-quantifiable (NQ) values of plasma concentrations will be handled as follows:

- If, at a given time point, 50% or less of the plasma concentrations are NQ, the mean, SD, geometric mean, %CV, and %GCV will be calculated by substituting the limit of quantification (LOQ) for values which are NQ.
- If more than 50%, but not all, of the concentrations are NQ, the mean, geometric mean, SD, %CV, and %GCV will be reported as not calculable (NC).
- If all the concentrations are NQ, the geometric mean and mean will be reported as NQ and the SD, %CV, and %GCV as NC.

The PK parameters will be rounded for reporting purposes both in the summary tables and by-patient listings. For the calculation of descriptive statistics and the statistical analysis, rounded values as presented in the data listings will be used. Except for raw measurements (such as C_{max} and t_{max}), all other derived PK parameters will be reported to 3 significant digits.

The PK data will be presented by treatment (olaparib 300 mg, olaparib 100 mg, olaparib 100 mg + paclitaxel) for single and multiple dosing separately. Note Cohort 2 has two multiple

dose summaries (one for olaparib 100 mg monotherapy and one for olaparib 100 mg in combination with paclitaxel). The data from Group 2 will be used to assess whether receiving olaparib in combination with paclitaxel has an impact on the pharmacokinetics of olaparib by calculating the treatment ratios of the geometric least-squares means with corresponding 95% CIs for $C_{max, ss}$, $C_{min, ss}$ and AUC_{ss} (combination:monotherapy). These will be calculated using mixed-effects models on the log-transformed pharmacokinetic parameters with fixed effects for treatment and random effect for patient.

All data will be summarised and listed appropriately.

No formal statistical analysis will be performed. The primary PK outcome variables will be summarised only.

12.2.3 Safety

Safety analyses will be presented using the safety analysis set and will be done by means of descriptive statistics. Safety profiles will be assessed in terms of AEs, vital signs (including BP and pulse rate), ECG, laboratory data (clinical chemistry, haematology and urinalysis) and physical examinations.

Appropriate summaries of AEs, laboratory data, vital signs, and ECGs will be produced. Adverse events will be summarised at the end of Parts A and B of the study respectively. Laboratory data, vital signs, body temperature, and ECGs will be summarised similarly at the end of Part A and Part B respectively. For physical examination, Baseline data will be summarized and post baseline data will be listed only. Summaries will be presented for scheduled visits only. Any unscheduled assessments will be listed. The baseline value is defined as the latest result obtained prior to the start of study treatment.

The number of patients experiencing AEs following administration of olaparib as well as the number of AEs experienced will be summarised. Adverse events will be classified using the MedDRA system of nomenclature (preferred term and system organ class [SOC] and preferred term [PT]). Adverse events reported before administration of olaparib will be listed only and be referred to as “pre-treatment”.

TEAE will be defined as an AE with the start date on or after the first dose date and up to (and including) 30 days after the last dose date.

TEAE for Part A will be defined as above but with the following distinctions:

- For patients who enter Part B, up to (not including) the date of the first dose of Part B,
- Or, for patients who do not enter Part B, up to (and including) 30 days after the last dose date.

Similarly, the number of patients experiencing SAEs, OAEs, AEs that led to withdrawal, AEs that led to death, and treatment-related AEs and the number of such events will be summarised at the end of each part of study, as applicable.

All AE data will be listed for all patients. In addition, SAEs, OAEs, and AEs that led to withdrawal or death, and treatment-related AEs will be listed.

Laboratory data (clinical chemistry, haematology, and urinalysis) will be summarised and listed. Shift tables will be provided for select tests, where shift from baseline to the worst value within each part of the study and overall will be summarised. Laboratory data outside the reference ranges should be indicated in the listings.

Concomitant medications will be summarised by the coded terms. The number of patients receiving a medication will be summarised overall and by cohort at the end of each part of the study. A medication taken during the course of the study is considered concomitant. A patient is only counted once if receiving the medication more than once.

The remaining safety variables will be presented using summary statistics for quantitative data and frequency counts for qualitative parameters.

All data will be summarised and listed appropriately.

The impact of any major protocol deviations, missing data and the use of rescue or concomitant medication on the robustness of study results will be investigated and any methods employed to deal with these will be documented.

Additional tables, figures, or listings may be produced to aid interpretation.

Further details of summaries of the safety data will be given in the SAP.

12.3 Determination of sample size

The sample size for the study is 30 patients, dosed in two cohorts of 15 in order to obtain evaluable single and multiple dose pharmacokinetic data from 12 patients in each cohort.

There is no formal sample size calculation, but as per CFDA guidance, 8 to 12 evaluable patients should be recruited. It is estimated that no more than 15 patients in each cohort is needed to ensure evaluable patient number suggested by CFDA (China SFDA Technical Guidance of Conducting Clinical Pharmacokinetics Studies for Chemical Entities 2005).

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.4.**

In the case of a medical emergency the investigator may contact the Clinical Development Manager (Study Team Leader). If the Study Leader is not available, contact the Study Physician at AstraZeneca Research and Development site shown below.

Name	Role in the study	Address & telephone number
[redacted]	Clinical Development Manager responsible for the Operation at central R&D site	AstraZeneca China China Clinical Operational Hub 3/F, Building 7, Lane 898, HaLei Road, Shanghai 201203, P.R. China [redacted]
[redacted]	SDT Physician responsible for the protocol	AstraZeneca Global Commercial – China R&D Medical Aff-ONC 26th floor, International Fortune Centre, No.8th Jian Guo Men Wai Avenue, Chao Yang District, Beijing, P.R. China. 100022 [redacted]

13.2 Overdose

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.3.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.3.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for three months following the last dose.

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until three months after the last dose should be followed up and documented.

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Clinical Study Protocol Appendix B

Drug Substance	Olaparib (AZD2281)
Study Code	D081BC00002
Edition Number	2
Date	05 Nov 2015

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C

Drug Substance	Olaparib (AZD2281)
Study Code	D081BC00002
Edition Number	2
Date	05 Nov 2015

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- Are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B

- Are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations

- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**

- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**

- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample

containment standards are encouraged wherever possible when road or rail transport is used.

AstraZeneca

Clinical Study Protocol Appendix D	
Drug Substance	Olaparib (AZD2281)
Study Code	D081BC00002
Edition Number	2
Date	05 Nov 2015

Appendix D
List of Drugs that May Have Potential CYP3A4 Interactions

LIST OF DRUGS THAT MAY HAVE POTENTIAL CYP3A4 INTERACTIONS

http://ctep.cancer.gov/protocolDevelopment/docs/cyp3a4.doc

CYP3A4 Substrates

Albuterol
Alfentanil
Alprazolam
Amiodarone
Amlodipine
Amprenavir
Aprepitant
Aripiprazole
Atazanavir
Atorvastatin
Benzphetamine
Bisoprolol
Bortezomib
Bosentan
Bromazepam
Bromocriptine
Budesonide
Buprenorphine
Buspirone
Busulfan
Carbamazepine
Cerivastatin
Chlordiazepoxide
Chloroquine
Chlorpheniramine
Cilostazol
Cisapride
Citalopram
Clarithromycin
Clobazam
Clonazepam
Clorazepate
Cocaine
Colchicine
Conivaptan
Cyclophosphamide
Cyclosporine
Dantrolene
Dapsone
Dasatinib (1)
Delavirdine
Diazepam
Dihydroergotamine
Diltiazem
Disopyramide
Docetaxel
Doxepin
Doxorubicin
Doxycycline
Efavirenz
Eletriptan
Enalapril
Eplerenone
Ergoloid mesylates
Ergonovine
Ergotamine
Erythromycin
Escitalopram
Estradiol
Estrogens, conj., synthetic
Estrogens, conj., equine
Estrogens, conj., esterified
Estrone
Estropipate
Ethinyl estradiol
Ethosuximide
Etoposide
Exemestane
Felbamate
Felodipine
Fentanyl
Flurazepam
Flutamide
Fluticasone
Fosamprenavir
Gefitinib
Haloperidol
Ifosfamide
Imatinib
Indinavir
Irinotecan
Isosorbide
Isosorbide dinitrate
Isosorbide mononitrate
Isradipine
Itraconazole
Ketamine
Ketoconazole
Lansoprazole
Letrozole
Levonorgestrel
Lidocaine
Losartan
Lovastatin
Medroxyprogesterone
Mefloquine
Mestranol
Methadone
Methylergonovine
Methysergide
Miconazole
Midazolam
Miglustat
Mirtazapine
Modafinil
Montelukast
Moricizine
Nateglinide
Nefazodone
Nelfinavir
Nevirapine
Nicardipine
Nifedipine
Nimodipine
Nisoldipine
Norethindrone
Norgestrel
Ondansetron
Paclitaxel
Pergolide
Phencyclidine
Pimozide
Pipotiazine
Primaquine
Progesterone
Quetiapine
Quinidine
Rabeprazole
Ranolazine
Repaglinide
Rifabutin
Ritonavir
Salmeterol
Saquinavir
Sibutramine
Sildenafil
Simvastatin
Sirolimus
Spiramycin
Sufentanil
Sunitinib
Tacrolimus
Tamoxifen
Tamsulosin
Telithromycin
Teniposide
Tetracycline
Theophylline
Tiagabine
Ticlopidine
Tipranavir
Tolterodine
Toremifene
Trazodone
Triazolam
Trimethoprim
Trimipramine
Troleandomycin
Vardenafil
Venlafaxine
Verapamil
Vinblastine
Vincristine
Vinorelbine
Zolpidem
Zonisamide
Zopiclone

CYP3A4 Inhibitors

Acetominophen
Acetazolamide
Amiodarone
Amlodipine
Amprenavir
Anastrozole
Aprepitant
Atazanavir
Atorvastatin
Azelastine
Azithromycin
Betamethasone
Bortezomib
Bromocriptine
Caffeine
Cerivastatin
Chloramphenicol
Chlorzoxazone
Cimetidine
Ciprofloxacin
Cisapride
Clarithromycin
Clemastine
Clofazimine
Clotrimazole
Clozapine
Cocaine
Conivaptan
Cyclophosphamide
Cyclosporine
Danazol
Dasatinib (1)
Delavirdine
Desipramine
Dexmedetomidine
Diazepam
Diclofenac Dihydroergotamine
Diltiazem
Disulfiram
Docetaxel
Doxorubicin
Doxycycline
Drospirenone
Efavirenz
Enoxacin
Entacapone
Ergotamine
Erythromycin
Ethinyl estradiol
Etoposide
Felodipine
Fentanyl
Fluconazole
Fluoxetine
Fluvastatin
Fluvoxamine
Fosamprenavir
Glyburide
Grapefruit juice (2)
Haloperidol
Hydralazine
Ifosfamide
Imatinib
Indinavir
Irbesartan
Isoniazid
Isradipine
Itraconazole
Ketoconazole
Lansoprazole
Lidocaine
Lomustine
Losartan
Lovastatin
Mefloquine
Mestranol
Methadone
Methimazole
Methoxsalen
Methylprednisolone
Metronidazole
Miconazole
Midazolam
Mifepristone
Mirtazapine
Mitoxantrone
Modafinil
Nefazodone
Nelfinavir
Nevirapine
Nicardipine
Nifedipine
Nisoldipine
Nizatidine
Norfloxacin
Olanzapine
Omeprazole
Orphenadrine
Oxybutynin
Paroxetine
Pentamidine
Pergolide
Phencyclidine
Pilocarpine
Pimozide
Pravastatin
Prednisolone
Primaquine
Progesterone
Propofol
Propoxyphene
Quinidine
Quinine
Quinupristin
Rabeprazole
Ranolazine
Risperidone
Ritonavir
Saquinavir
Selegiline
Sertraline
Sildenafil
Sirolimus
Sulconazole
Tacrolimus
Tamoxifen
Telithromycin
Teniposide
Testosterone
Tetracycline
Ticlopidine
Tranylcypromine
Trazodone
Troleandomycin
Valproic acid
Venlafaxine
Verapamil
Vinblastine
Vincristine
Vinorelbine
Voriconazole
Zafirlukast
Ziprasidone

CYP3A4 Inducers

Aminoglutethimide
Carbamazepine
Fosphenytoin
Nafcillin
Nevirapine
Oxcarbazepine
Pentobarbital
Phenobarbital
Phenytoin
Primidone
Rifabutin
Rifampin
Rifapentine
St. John's wort (3)

When drugs classified as 'substrates' are co-administered with *olaparib*, there is the potential for higher concentrations of the 'substrate'. When *olaparib* is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of *olaparib* is the potential outcome. The co-administration of 'inducers' would potentially lower plasma *olaparib* concentrations.

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.

Only major substrates and effective inducers are listed.

Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

(1) Investigator's Brochure: Dasatinib (BMS 354825). Bristol-Myers Squibb. October 2006.

(2) Malhotra *et al*. (2001). Clin Pharmacol Ther. 69:14-23.

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Clinical Study Protocol Appendix E	
Drug Substance	Olaparib (AZD2281)
Study Code	D081BC00002
Edition Number	2
Date	05 Nov 2015

Appendix E
Acceptable Birth Control Methods

ACCEPTABLE BIRTH CONTROL METHODS

Olaparib is regarded as a compound with medium/high foetal risk

- Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

- Male patients and their partners, who are sexually active and of childbearing potential, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], throughout the period of taking study treatment and for 3 months after last dose of study drug(s) due to the unknown effects of the study drug on the sperm, or they must totally/truly abstain from any form of sexual intercourse (see below). Male patients should not donate sperm throughout the period of taking study treatment and for 3 months following the last dose of study drug(s).

Acceptable Non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must continue for the total duration of study treatment and for at least 1 month after the last dose and for 3 months after last dose for male patients. Periodic abstinence (e.g., calendar ovulation, symptothermal post ovulation methods) and withdrawal are not acceptable methods of contraception.

- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.

- Tubal occlusion PLUS male condom

- IUD PLUS male condom. Provided coils are copper-banded

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (eg., Depo-Provera) PLUS male condom
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom
- Norelgestromin / EE transdermal system PLUS male condom
- Intrauterine system [IUS] device (eg., levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom

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Clinical Study Protocol Appendix F	
Drug Substance	Olaparib (AZD2281)
Study Code	D081BC00002
Edition Number	2
Date	05 Nov 2015

Appendix F
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥ 3x ULN **and** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (See Section 6)
- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to

determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required
  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described is Section 4.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease or did the patient meet PHL criteria prior

to starting study treatment and at their first on study treatment visit as described in Section 6.

If No: follow the process described in Section 4.2 of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

8. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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Clinical Study Protocol Appendix G	
Drug Substance	Olaparib (AZD2281)
Study Code	D081BC00002
Edition Number	2
Date	05 Nov 2015

Appendix G
Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.