AstraZeneca

Revised Clinical Study Protocol

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0816C00005
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An Open-label, Non-randomised, Multicentre, Comparative, Phase I Study to Determine the Pharmacokinetics, Safety and Tolerability of Olaparib following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumours and Normal Hepatic Function or Mild or Moderate Hepatic Impairment

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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	23 August 2013		
2	06 December 2013		
3	23 October 2014		
4	11 August 2015		

5	11 March 2016		
Administrative change No.	**Date of Administrative Change**	**Local Administrative change No.**	**Date of local Administrative Change**
1	18 June 2013		

AstraZeneca

PROTOCOL SYNOPSIS

An Open-label, Non-randomised, Multicentre, Comparative, Phase I Study to Determine the Pharmacokinetics, Safety and Tolerability of Olaparib following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumours and Normal Hepatic Function or Mild or Moderate Hepatic Impairment

International Co-ordinating Investigator

[redacted]
Belgium

Study centre(s) and number of patients planned

This study will be conducted at approximately 20 sites in Europe, with the possibility of sites in North America and Asia, with approximately 30 patients enrolled and at least 24 evaluable patients required.

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2013	I
Estimated date of last patient completed (Part A)	Q3 2016	
Estimated date of last patient completed (Part B)	Q3 2017	

Objectives

The primary objective of this study is to investigate the pharmacokinetics (PK) of olaparib after a single oral dose of 300 mg to patients with advanced solid tumours and mild or moderate hepatic impairment compared to those with normal hepatic function.

The secondary objective is to investigate the safety and tolerability of single and multiple oral doses of olaparib in advanced solid tumour patients with mild or moderate hepatic impairment and in those with normal hepatic function.

The exploratory objective of this study is to explore changes in protein binding of olaparib and the subsequent effects on its PK in patients with varying degrees of hepatic function.

Study design

This is a 2-part study in patients with advanced solid tumours. Part A will investigate the PK of olaparib in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function; Part B will allow patients with mild or moderate hepatic impairment or normal hepatic function continued access to olaparib after the PK phase and will provide additional safety data. Patients with normal hepatic function and mild hepatic impairment will be recruited before those with moderate hepatic impairment. At least 3 months of safety data (and PK data if available) from at least 3 patients with mild hepatic impairment will be reviewed before recruiting patients with moderate hepatic impairment into the study, first in Part A and then in Part B. If the safety, tolerability and PK data from the 3 patients with mild hepatic impairment dosed continuously with olaparib for 3 months raises safety concerns for the continuous dosing of patients with moderate hepatic impairment, then patients with moderate hepatic impairment will not enter the study.

Approximately 30 patients are planned to be enrolled with at least 24 evaluable patients required to complete Part A (8 patients with normal hepatic function, 8 with mild hepatic impairment [Child-Pugh A] and 8 with moderate hepatic impairment [Child-Pugh B]). An evaluable patient is defined as a patient having full PK sampling to 96 hours post-dose of olaparib. Groups will be recruited so that, if possible, at least 3 patients of each sex are in each group.

Part A is an open-label, parallel group, PK study. Each patient will receive a single oral dose of olaparib 300 mg (given via the tablet formulation). Where possible, patients will check into the clinic on Day –1, the evening prior to dosing (Day 1), remain resident until 24 hours after the dose of olaparib (Day 2), and then return to the clinic for assessments on Day 3 (48 hours), Day 4 (72 hours) and Day 5 (96 hours).

Blood samples for the determination of olaparib will be collected during Part A.

On completion of Part A, patients may be entered into Part B and continue to take olaparib tablets (300 mg twice daily [bd]) if they and the investigator agree that this is appropriate, providing the baseline safety assessments for Part B are in accordance with the study inclusion and exclusion criteria.

Patients must start Part B within 2 weeks (minimum 5 days, maximum 14 days) of dosing in Part A. Patients will have weekly clinic visits for the first 4 weeks; thereafter visits will be every 4 weeks. Part B will be of 12 months' duration from the date the last patient enters this part of the study.

During and after Part B, patients may continue to take olaparib, if they and the investigator deem it appropriate, until such time as their disease progresses, the investigator believes they are no longer deriving clinical benefit, or they stop taking olaparib for any other reason. After

the end of Part B, patients will be seen as per their normal routine clinical schedule and no clinical data will be collected, other than serious adverse events (SAEs).

Patients will return to the clinic for follow-up assessments either 30 days (±7 days) after their last dose in the last treatment period in Part A or 30 days (±7 days) after discontinuation of olaparib in Part B. If a patient discontinues investigational product (IP) during Part B, they will also attend a study treatment discontinuation visit.

Target patient population

Patients aged ≥18 years with advanced solid tumours who are refractory or resistant to standard therapy will be recruited. For inclusion in the study as a patient with hepatic impairment, patients must have stable mild hepatic impairment, as defined by the Child-Pugh Classification system, for at least 1 month prior to the start of the study, or stable moderate hepatic impairment, as defined by the Child-Pugh Classification system, for at least 2 weeks prior to the start of the study. For inclusion in the study as a patient with normal hepatic function, patients must have a negative result for serum hepatitis B surface antigen and hepatitis C antibody.

Investigational product, dosage and mode of administration

In Part A, each patient will receive a single 300 mg oral dose of olaparib (administered as 2 x 150 mg tablets).

In Part B, patients will receive 300 mg oral olaparib (administered as 2 x 150 mg tablets) bd for the duration of their participation.

Comparator, dosage and mode of administration

None.

Duration of treatment

In Part A, each patient will receive a single 300 mg oral dose of olaparib.

In Part B, patients will receive 300 mg oral olaparib bd for the duration of their participation.

Outcome variables:

- **Pharmacokinetics (primary variables)**

In Part A, the following variables will be calculated for olaparib where the data allow: maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), area under the plasma concentration time curve from zero to the last measureable time point (AUC_{0-t}), area under the plasma concentration time curve from zero to infinity (AUC), apparent clearance following oral administration (CL/F), terminal half-life ($t_{½}$), apparent volume of distribution (V_z/F) and terminal rate constant (λ_z).

Pharmacokinetics will not be measured in Part B.

- **Safety**

Assessment of adverse events (AEs) graded by Common Terminology Criteria for Adverse Events (CTCAE) v4.0, standard 12-lead electrocardiograms (ECGs), physical examination, vital signs (including blood pressure, pulse), and evaluation of laboratory parameters (clinical chemistry, haematology, and urinalysis).

- **Exploratory**

In Part A, plasma protein binding at 1 hour after dosing, used to calculate free C_{max} (C_{max} of unbound olaparib), free AUC (AUC of unbound olaparib) and unbound CL/F (CL/F of unbound olaparib).

Statistical methods

The study has been sized to provide adequate PK information to assess the effects of hepatic impairment on the PK of olaparib, whilst exposing as few patients as possible to the IP and procedures. Based on the estimate of between-patient standard deviation (SD) for log AUC from Study D0810C00024 of 0.531 including 8 patients per arm provides approximately 80% chance that a 1-sided 95% confidence interval would exclude the possibility of a doubling in AUC.

All patients who receive an olaparib dose and have full PK sampling up to 96 hours post-dose will be included in the PK analysis set. All patients who receive at least 1 dose of olaparib and for whom any post-dose data are available will be included in the safety population.

The goal of the statistical analysis in Part A is to estimate the effect of hepatic function on the PK of olaparib. Following log-transformation, C_{max} and AUC (or AUC_{0-t}, if AUC is not adequately estimable) of olaparib will be separately analysed by analysis of variance (ANOVA), fitting a term for hepatic function group (moderate hepatic impairment, mild hepatic impairment or normal hepatic function).

The results of these analyses will be presented in terms of geometric means for each hepatic function group. The ratio of geometric means of each hepatically impaired group compared to the normal group (mild/moderate: controls) will be presented with the respective 1-sided 95% upper confidence limit.

The possibility that hepatic impairment has a clinically relevant effect on the exposure of olaparib will be considered if the upper 1-sided 95% confidence limit for the ratio does not lie below the limit of 2.

Safety data will be listed and summarised using descriptive statistics.

An interim analysis will be performed once all patients in the normal hepatic function and mild hepatic impairment groups have completed Part A. The interim PK analysis will be as described above, but limited to a comparison between the normal hepatic function and mild hepatic impairment groups.

Any patients enrolled into the moderate hepatic impairment group at the time of data-cut off for this interim analysis will be listed but not summarised. The data will be displayed, in both the tables and listings, by hepatic group and will include a total column for an overall summary. Summary tables will display mild hepatic impairment and normal hepatic function while listings will also display the moderate hepatic impairment group.

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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
AE	Adverse event (see definition in Section 6.4.1)
AFP	α fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under plasma concentration-time curve from zero to infinity
AUC_{0-t}	Area under plasma concentration-time curve from zero to the last measurable time point
bd	Twice daily (Latin: *bis die*)
BP	Blood pressure
BRCA	Breast cancer gene, ie, BRCA1 and BRCA2
BUN	Blood urea nitrogen
CI	Confidence interval
CL/F	Apparent plasma clearance following oral administration
C_{max}	Maximum plasma drug concentration
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSF	Colony-stimulating factor
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CV	Coefficient of variation
DAE	Discontinuation of Investigational Product due to Adverse Event
DNA	Deoxyribonucleic acid

Abbreviation or special term	Explanation
DSBs	Double strand breaks
E-code	Enrolment number code
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
%GCV	Geometric %CV
GGT	Gamma glutamyltransferase
GMP	Good Manufacturing Practice
HCC	Hepatocellular carcinoma
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
INR	International normalised ratio
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational product
LDH	Lactate dehydrogenase
LOQ	Limit of quantification
LPI	Last patient in
LSLV	Last subject last visit
λ_z	Terminal rate constant
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NC	Not calculable

Abbreviation or special term	Explanation
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NQ	Non quantifiable
OAE	Other Significant Adverse Event (see definition in Section 11.1.1)
PARP	Polyadenosine 5'-diphosphoribose polymerase
PI	Principal Investigator
PK	Pharmacokinetics
RBC	Red blood cells
SAE	Serious adverse event (see definition in Section 6.4.2).
SAP	Statistical analysis plan
SD	Standard deviation
SSBs	Single strand breaks
$t_{½}$	Terminal half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach maximum plasma concentration
ULN	Upper limit of normal (range)
V_z/F	Apparent volume of distribution
WBC	White blood cells
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Investigators should be familiar with the current olaparib Investigator Brochure (IB).

Olaparib (AZD2281, KU-0059436) is a potent polyadenosine 5'diphosphoribose [poly (ADP ribose] polymerisation (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

PARP inhibition is a novel approach to targeting tumours with deficiencies in deoxyribonucleic acid (DNA) repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair. Tumours with homologous recombination repair deficiencies (HRD), such as ovarian cancers in patients with breast cancer gene (BRCA)1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

Olaparib has been shown to inhibit selected tumour cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies. Cells deficient in homologous recombination DNA repair factors, notably BRCA1/2, are particularly sensitive to olaparib treatment.

1.1.1 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the olaparib IB.

1.1.2 Toxicology and safety pharmacology summary

Olaparib has been tested in a standard range of safety pharmacology studies, eg, dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetised dog or any behavioural, autonomic, or motor effects in the rat at the doses studied.

Rodent and dog toxicology studies have indicated that the primary target organ of toxicity is the bone marrow with recovery seen following withdrawal of olaparib. Ex vivo studies have confirmed that olaparib is cytotoxic to human bone marrow cells.

Olaparib was not mutagenic in the Ames test but was clastogenic in the Chinese hamster ovary (CHO) chromosome aberration test in vitro. When dosed orally, olaparib also induced micronuclei in the bone marrow of rats. This profile is consistent with the potential for genotoxicity in man.

Reproductive toxicology data indicate that olaparib can have adverse effects on embryofoetal survival and development at dose levels that do not induce significant maternal toxicity.

Further information can be found in the current version of the olaparib IB.

1.1.3 Clinical experience

The clinical experience with olaparib is fully described in the current version of the olaparib IB.

1.1.3.1 Patient experience

The Phase II study D0810C00019 demonstrated the efficacy of olaparib maintenance therapy when using the capsule formulation (8 capsules twice daily [bd]). A more patient-friendly tablet formulation (2 tablets bd) has been developed and the Phase III study D0816C00002 will investigate the efficacy of the tablet formulation, 300 mg bd, when given as a maintenance therapy to BRCA mutated platinum sensitive relapsed ovarian cancer patients. This tablet dose has been chosen based on data from an ongoing study, D0810C00024. Since it has been shown that the capsule and tablet formulations are not bioequivalent a formulation switch based on bioequivalence has not been possible. The tablet dose of 300 mg bd has been shown to have similar efficacy in terms of tumour shrinkage in BRCA mutated ovarian cancer patients to the 400 mg bd capsule together with an acceptable tolerability profile.

The tolerability profile of the 300 mg bd tablet dose in Study D0810C00024 was considered similar to the 400 mg bd capsule formulation. The most common adverse events (AEs) were consistent with the known safety profile of olaparib, namely low grade nausea, vomiting, fatigue and anaemia. Further information is provided in the IB.

1.1.3.2 Clinical pharmacokinetics

Following administration of single oral doses of the tablet formulation at doses of 25, 50 and 250 mg (n=6 per cohort), absorption was rapid and slightly more rapid than seen following the capsule dose. The maximum plasma concentration (C_{max}) was typically achieved between 0.5 hours and 2 hours after dosing. Following the peak, plasma concentrations declined biphasically with a terminal $t_{½}$, across all 3 dose levels, of between 5 hours and 9 hours (average=6.97 hours ±1.03 standard deviation [SD]). Both geometric mean C_{max} and area under the plasma concentration-time curve from zero to infinity (AUC) increased approximately proportionally with dose (8-fold and 12-fold, respectively, for a 10-fold increase in dose). The mean volume of distribution (V_z/F) of olaparib was 54.9 L±30.2 SD and the mean plasma clearance (CL/F) was 5.42 L/h±2.62 SD.

A preliminary analysis of the effect of food (a light snack) on the pharmacokinetics (PK) of olaparib tablets was also investigated in Study D0810C00024 and preliminary analysis of this data suggest that the intake of a light snack does not impact the PK of olaparib. Patients will be allowed to take olaparib tablets with a light snack during the Phase III study.

Further information on the PK and metabolism of olaparib is provided in the current version of the IB.

1.2 Research hypothesis

There are no clinically significant changes in the PK of olaparib when administered to patients with mild or moderate hepatic impairment compared to patients with normal hepatic function.

1.3 Rationale for conducting this study

Material was excreted in both the urine and faeces as a combination of unchanged drug and metabolite, thus indicating the importance of the metabolic route in the clearance of olaparib. In vitro, the metabolism of olaparib has been shown to be predominantly via CYP3A4. Since patients with breast or ovarian cancer may suffer from varying degrees of hepatic impairment, it is important to define the effects of hepatic impairment on the PK of olaparib in order to determine the need to develop dose adjustment recommendations; this will be investigated in Part A of this study.

Safety and tolerability data will be collected as per regulatory and ethical guidelines and to expand the safety/tolerability database for patients with advanced solid malignancies treated with oral olaparib tablets.

Part B will allow patients who have participated in Part A to receive a therapeutic dose of olaparib on a continuous basis and therefore possibly gain clinical benefit. Safety and tolerability data collected in Part B will add to the safety database for patients with advanced solid malignancies treated with oral olaparib.

1.4 Benefit/risk and ethical assessment

This study is robustly designed to assess the primary objective while minimising the number of patients exposed to olaparib. AstraZeneca believes that olaparib continues to demonstrate an overall positive benefit-risk balance to support its further clinical development. Pre-clinical and emerging clinical tolerability data from patients indicate that olaparib is generally well tolerated by patients with advanced cancer (please refer to the IB for details).

All AEs, vital signs, and laboratory data will be collected and reviewed by the Principal Investigator (PI) and clinical research staff on an ongoing basis.

Although patients may not initially gain any benefit from participation in Part A of the study due to the short dosing period, some benefit may be gained in Part B. If the investigator believes it is in the patient's interest, they may continue treatment with olaparib until such time as their disease progresses, the investigator believes they are no longer deriving clinical benefit, or they stop taking the olaparib for any other reason. Patients with normal hepatic function and mild hepatic impairment will be recruited before those with moderate hepatic impairment. At least 3 months of safety data (and PK data if available) from at least 3 patients with mild hepatic impairment will be reviewed before recruiting patients with moderate hepatic impairment into the study, first in Part A and then in Part B. If the safety, tolerability and PK data from the 3 patients with mild hepatic impairment dosed continuously with olaparib for 3 months raises safety concerns for the continuous dosing of patients with

moderate hepatic impairment, then patients with moderate hepatic impairment will not enter the study.

The data generated from this study will support further development of olaparib for the treatment of cancer. The benefit/risk assessment for the conduct of this study of olaparib in patients is acceptable.

2. STUDY OBJECTIVES

2.1 Primary objective

Table 1 Primary objective

Primary objective	Primary outcome variables
To investigate the pharmacokinetics of olaparib after a single oral dose of 300 mg to patients with advanced solid tumours and mild or moderate hepatic impairment compared to those with normal hepatic function.	Maximum plasma concentration (C_{max}), area under the plasma concentration time curve from zero to the last measureable time point (AUC_{0-t}), area under the plasma concentration time curve from zero to infinity (AUC), time to reach maximum plasma concentration (t_{max}), terminal half-life ($t_{½}$), apparent clearance following oral administration (CL/F), apparent volume of distribution (V_z/F) and terminal rate constant (λ_z).

2.2 Secondary objectives

Table 2 Secondary objective

Secondary objective	Secondary outcome variables
To investigate the safety and tolerability of single and multiple oral doses of olaparib in advanced solid tumour patients with mild or moderate hepatic impairment and in those with normal hepatic function.	Assessment of AEs, graded by CTCAE (v4.0), physical examination, vital signs (including BP and pulse) standard 12-lead ECG and evaluation of laboratory parameters (clinical chemistry, haematology and urinalysis).

BP blood pressure; CTCAE Common Terminology Criteria for Adverse Events; ECG electrocardiogram

2.3 Exploratory objectives

Table 3 Exploratory objective

Exploratory objective	Exploratory outcome variables
To explore changes in protein binding of olaparib and the subsequent effects on its PK in patients with varying degrees of hepatic function.	In Part A, Plasma protein binding at 1 hour after dosing, used to calculate free C_{max} (C_{max} of unbound olaparib), free AUC (AUC of unbound olaparib) and unbound CL/F (CL/F of unbound olaparib).

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a 2-part study in patients with advanced solid tumours. Part A will investigate the PK of olaparib in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function; Part B will allow patients continued access to olaparib after the PK phase and will provide additional safety data.

Approximately 30 patients are planned to be enrolled from approximately 20 sites in Europe, with the possibility of sites in North America and Asia, with at least 24 evaluable patients required to complete Part A (8 patients with normal hepatic function, 8 with mild hepatic impairment [Child-Pugh A] and 8 with moderate hepatic impairment [Child-Pugh B]). An evaluable patient is defined as a patient having full PK sampling to 96 hours post-dose of olaparib. Groups will be recruited so that, if possible, at least 3 patients of each sex are in each group. Patients with normal hepatic function and mild hepatic impairment will be recruited before those with moderate hepatic impairment. At least 3 months of safety data (and PK data if available) from at least 3 patients with mild hepatic impairment will be reviewed before recruiting patients with moderate hepatic impairment into the study, first in Part A and then in Part B. If the safety, tolerability and PK data from the 3 patients with mild hepatic impairment dosed continuously with olaparib for 3 months raises safety concerns for the continuous dosing of patients with moderate hepatic impairment, then patients with moderate hepatic impairment will not enter the study.

Part A is an open-label, parallel group, PK study comparing patients with mild or moderate hepatic impairment to patients with normal hepatic function. Each patient will receive a single oral dose of olaparib 300 mg (given via the tablet formulation). Where possible, patients will check into the clinic on Day -1, the evening prior to dosing (Day 1), remain resident until 24 hours after the dose of olaparib (Day 2), and then return to the clinic for assessments on Day 3 (48 hours), Day 4 (72 hours) and Day 5 (96 hours). The overall study plan for Part A of the study is provided in Table 4.

Blood samples for the determination of olaparib will be collected during Part A. Full details of the blood PK sampling times are provided in Table 5.

On completion of Part A, patients may be entered into Part B and continue to take olaparib tablets (300 mg bd) if they and the investigator agree that this is appropriate, providing the baseline safety assessments for Part B are in accordance with the study inclusion and exclusion criteria and patients continue to meet the criteria for mild or moderate hepatic impairment or normal hepatic function.

Patients must start Part B within 2 weeks (minimum 5 days, maximum 14 days) of dosing in Part A. Patients will have weekly clinic visits for the first 4 weeks; thereafter visits will be every 4 weeks. Assessments will be conducted as shown in Table 6. Part B will be of 12 months' duration from the date the last patient enters this part of the study.

During and after Part B, patients may continue to take olaparib, if they and the investigator deem it appropriate, until such time as their disease progresses, the investigator believes they are no longer deriving clinical benefit, or they stop taking olaparib for any other reason. After the end of Part B (12 months after the last patient entered Part B), patients will be seen as per their normal routine clinical schedule and no clinical data will be collected, other than serious adverse events (SAEs).

Patients will return to the clinic for follow-up assessments either 30 days (±7 days) after their last dose in the last treatment period in Part A or 30 days (±7 days) after discontinuation of olaparib in Part B. If a patient discontinues investigational product (IP) during Part B, they will also attend a study treatment discontinuation visit.

A flow chart of Part A of the study is illustrated in Figure 1.

Figure 1 Study flow chart (Part A)

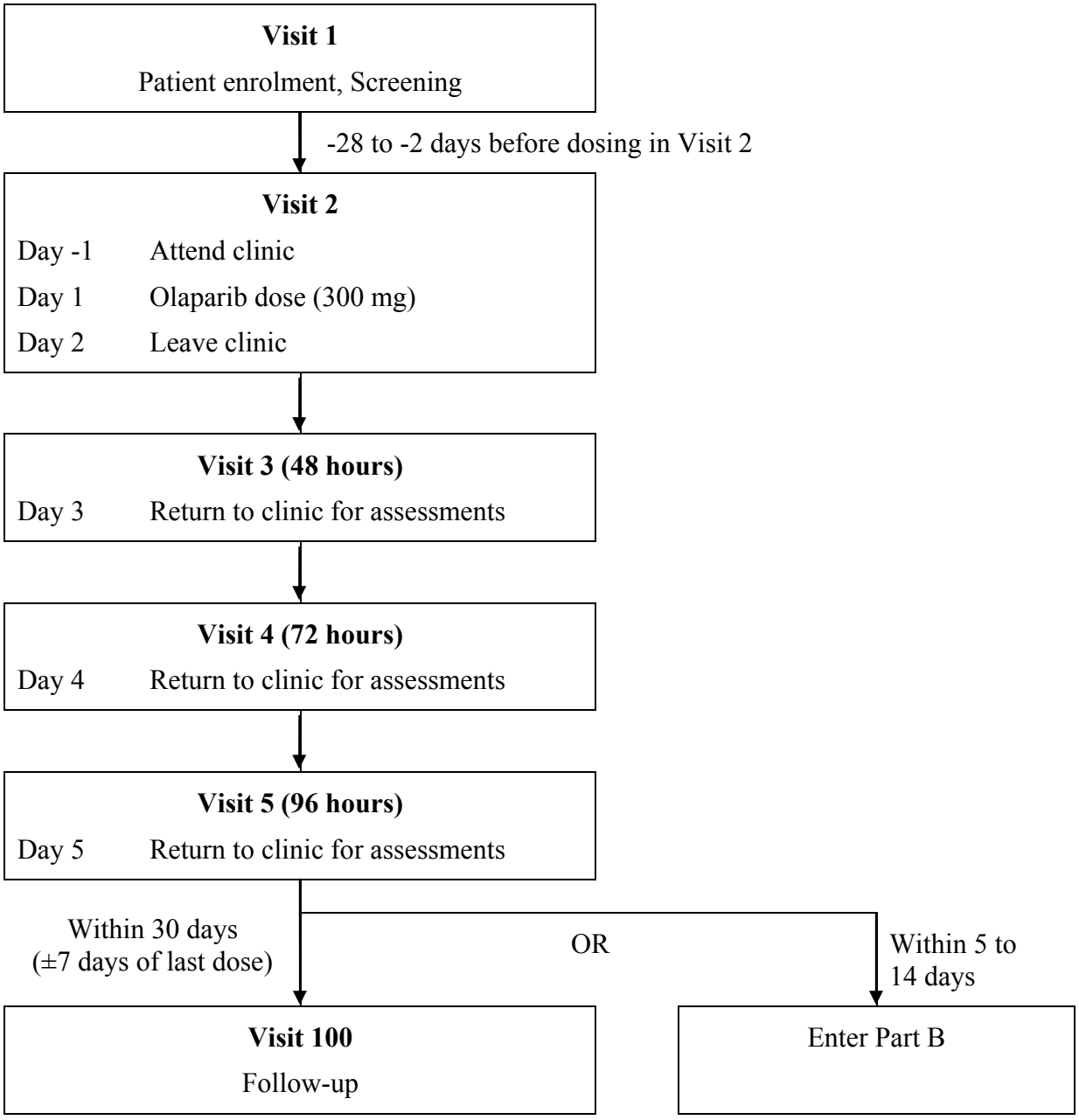

Table 4 Study plan – Part A (PK study)

Assessments	**Screening**	**Treatment Period**						**Follow Up**[a]
Visits	**1**	**2**			**3**	**4**	**5**	**100**
Day[b]	**-28 to -2 days before dosing**	**-1**[b]	**1**	**2**	**3**	**4**	**5**	**30 (±7) days after last dose**
Resident in clinic		<---------->						
Outpatient visits	X				X	X	X	X
Written informed consent	X							
Demography	X							
Medical/surgical history	X							
Prior and concomitant meds	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria including classification of hepatic function	X	X	X					
Germline BRCA status[c]	X							
ECOG performance status	X							
Height and weight	X							
Physical examination	X	X						X
Vital signs (BP/pulse)	X		X[d]	X	X			X
Body temperature	X		X					
Resting standard 12-lead ECG	X		X[d]		X			X
HBV and HCV Serology[e]	X							
Haematology/coagulation[f]/ biochemistry	X	X			X			X
Urinalysis[g]	X	X			X			X
Serum/urine pregnancy test[h]	X		X					
Olaparib administration			X					
Protein binding sample[i]			X					
Olaparib PK blood sampling[j]			X	X	X	X	X	
Adverse events[k]	X	X	X	X	X	X	X	X

BP blood pressure; BRCA breast cancer gene; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; HBV hepatitis B virus; HCV hepatitis C virus; HR heart rate; PK pharmacokinetics

[a] For patients who withdraw from the study prematurely or do not participate in Part B

[b] There is no Day 0. Day 1 is the day of dosing; Day -1 is the day before dosing. All Day -1 procedures must be performed on Day -1 or pre-dose on Day 1. If the patient has been screened within 48 hours of Day 1, safety laboratory tests (haematology, coagulation, biochemistry and urinalysis) do not need to be repeated.

[c] Germline BRCA status to be collected on CRF, if known. If known, record whether patient is +ve or –ve for mutation. If +ve, record sequence.

[d] Pre-dose and 4 hours post-dose.

[e] Includes HBsAg (hepatitis B surface antigen), anti-HBs (anti-hepatitis B surface antigen), anti-HBc (anti-hepatitis B core antigen) and anti-HCV

[f] Coagulation (aPTT and INR) will be performed at baseline and if clinically indicated. For patients taking warfarin reference Section 5.6.3.

[g] Protein, blood, glucose and bilirubin.

[h] Pre-menopausal women of childbearing potential must have a negative urine or serum pregnancy test within 28 days prior to starting treatment and a confirmatory test before dosing on Day 1. In the event of a suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.

[i] Blood sample collected for protein binding analysis at 1 hour post-dose (see Table 5).

[j] Olaparib PK samples will be collected at pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 and 96 hours after olaparib dosing (see Table 5).

[k] If a patient withdraws for any reason, any ongoing study-related toxicity or SAE at discontinuation must be monitored until resolution. After discontinuation from treatment, patients must be followed up for any new AEs for 30 calendar days after last dose of IP. All existing and any new AEs occurring during the 30-day period must be recorded and followed to resolution if possible.

Table 5 Pharmacokinetic sampling – Part A (PK study)

Day	Time (h)	Dose	PK blood sample[a]	Protein binding sample[b]
1	Pre-dose		X	
	0	X		
	0.25		X	
	0.5		X	
	1		X	X
	1.5		X	
	2		X	
	3		X	
	4		X	
	6		X	
	8		X	
	12		X	
2	24		X	
3	48		X	
4	72		X	
5	96		X	

PK pharmacokinetic

[a] Venous blood samples (4 mL) for determination of olaparib in plasma.

[b] Protein binding sample (3 mL) to determine the free fraction of olaparib in plasma

Table 6 Study plan – Part B (continued access to olaparib)

Visit Number	**6**[a]	**7**	**8**	**9**	**10**	**Subsequent on-treatment visits every 4 weeks**[b] **Visit 11 onwards**	**Study treatment discontinued**	**Follow-up 30 (±7) days after last dose of study medication**
Day	1[a]	8	15	22	29	Day 1 of next visit period (Equals Day 57 [Week 9] then Day 85 [Week 13], etc)		
Visit window		±3d	±3d	±3d	±3d	±7d	±7d	±7d
Physical examination[c]	X							
Vital signs (BP, pulse, temperature)	X	X	X	X	X	X	X	X
ECOG performance status	X							
Resting standard 12-lead ECG	X					X		X
Haematology[d]/clinical chemistry	X[d]	X	X	X	X[d]	X[d]	X[d]	X[d]
Urinalysis[e]	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Previous and concomitant medications	X	X	X	X	X	X	X	X
Olaparib dispensed/returned[f]	X				X[e]	X[e]	X	

BP blood pressure; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group

Note: A pregnancy test will be conducted only in the event of a suspected pregnancy during the study.

[a] Baseline safety assessments must be in accordance with the study inclusion and exclusion criteria

[b] Visit to take place on Day 1 of a 4 week (28 day) visit period. Visits will continue for 12 months from the date the last patient enters Part B.

[c] After baseline, it is not necessary to record any physical examination details on the CRF; any clinically significant changes should be recorded as AEs.

[d] Haematology assessment to include prothrombin time for patients with mild or moderate hepatic impairment at every visit
Additional haematology assessments will be performed on Day 1, then monthly for 6 months, at discontinuation, and at the 30-day follow-up visit (see Section 6.4.5).

[e] Protein, blood, glucose and bilirubin. Urinalysis to be conducted at every visit for patients with hepatic impairment. After baseline, urinalysis is only required for patients with normal hepatic function if clinically indicated.

[f] Sufficient study treatment should be dispensed for at least each treatment period plus overage; however additional treatment can be dispensed to patients to last longer in accordance with local practice.

3.2 Rationale for study design, doses and control groups

This study has been designed to investigate the effects of hepatic impairment on the PK of olaparib. Multiple dose PK of olaparib have previously been shown to be predictable and following twice daily dosing of the tablet formulation there is little accumulation on multiple dosing, therefore a single dose study is justified. Patients' hepatic function will be classified based on the Child-Pugh Classification system, in accordance with CHMP guidance [CPMP/EWP/2339/02].

Patients with hepatic metastases and/or hepatocellular carcinoma (HCC) are eligible for the study, providing the hepatic metastases or HCC are not the sole reason for any changes in liver function satisfying the criteria for mild or moderate hepatic impairment as defined by the Child Pugh criteria. Patients must have globally impaired hepatic function to participate in the study as the type of hepatic impairment that affects drug disposition is more related to liver cirrhosis and fibrosis i.e. to factors affecting the ability of the drug to enter the hepatocyte, rather than drug metabolism per se. Hepatocellular carcinoma and hepatic metastases do not have the same effect on general hepatocyte permeability that is seen in global hepatic impairment (e.g. related to cirrhosis or fibrosis). Since the liver has very large capacity for drug metabolism, a reduction in the amount of healthy functioning liver (due to the presence of carcinoma/metastases) does not necessarily have any impact on drug clearance. For this reason, studies performed in patients with 'hepatic impairment solely due to liver metastases' are not considered to be valid hepatic impairment studies by regulatory authorities. The aim of the study is to look at the exposure of olaparib in patients with 'globally impaired hepatic function', hence the categorisation of the degree of impairment for an individual patient will be based upon Child-Pugh criteria.

The impact of hepatic impairment on protein binding of olaparib will also be studied, since plasma protein binding is often altered in patients with impaired hepatic function.

Due to existing pre-clinical toxicology data it is not possible to use healthy volunteers for this study and therefore the study is being conducted in patients with advanced solid tumours.

The tablet dose chosen will deliver exposure that has been previously demonstrated to be tolerated in cancer patients, and is the dose to be used in the monotherapy maintenance setting in Phase III.

Although the selected patient population includes patients with impaired hepatic function, based on pre-clinical and clinical data to date, there is no evidence that olaparib will compromise hepatic function further.

From completed olaparib studies to date, there are no safety concerns noted for the hepatic parameters measured. Serious adverse events associated with hepatic toxicity are low within the olaparib trial programme (<1% based on 2020 patients exposed to olaparib, April 2013). Serious adverse events relating to hepatobiliary disorders (<1.0%) include bile duct obstruction (n=2), bile duct stone (n=1), cholangitis (n=1), cholecystitis/cholecystitis acute

(n=2), hyperbilirubinaemia (n=1), elevation in ALT (n=2) or AST (n=1), increased bilirubin (n=1) and liver function test abnormal (n=1).

A full review of available laboratory data from 11 completed monotherapy studies in 975 patients treated with olaparib identified 11 potential Hy's Law cases defined as any situation where a patient had an increase in both AST or ALT ≥3xULN and total bilirubin ≥2xULN irrespective of alkaline phosphatase at any time point during the study. Following a full evaluation of these potential Hy's Law cases, alternative explanations or alternative causes for the hepatic laboratory findings can be found.

Based on available data to date, there is no evidence to suggest drug induced liver toxicity associated with olaparib exposure.

Due to the lack of clinical data and unknown risk benefit profile of dosing olaparib in oncology patients with moderately impaired hepatic function, patients with normal hepatic function and mild hepatic impairment will be recruited before those with moderate hepatic impairment. At least 3 months of safety data (and PK data if available) from at least 3 patients with mild hepatic impairment will then be reviewed before recruiting patients with moderate hepatic impairment into the study, first in Part A and then in Part B. If the safety, tolerability and PK data from the 3 patients with mild hepatic impairment dosed continuously with olaparib for 3 months raises safety concerns for the continuous dosing of patients with moderate hepatic impairment, then patients with moderate hepatic impairment will not enter the study.

Study sites in North America and Asia may also enrol patients. Olaparib PK in Western and Japanese patients are similar and there is not predicted to be different PK for patients from China, Taiwan or Korea.

4. PATIENT SELECTION CRITERIA

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

Each patient 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 **as a patient with hepatic impairment,** the following criterion must be met:

1. Patients must have stable **mild** hepatic impairment (as defined by Child-Pugh classification), for at least 1 month prior to the start of the study or stable **moderate** hepatic impairment (as defined by Child-Pugh classification), for at least 2 weeks prior to the start of the study (see Section 6.2.1.1). Patients with hepatic metastases and/or HCC are eligible for the study, providing the hepatic metastases or HCC are

not the sole reason for any changes in liver function satisfying the criteria for mild or moderate hepatic impairment as defined by the Child Pugh criteria. Patients must have globally impaired hepatic function to participate in the study.

For inclusion in the study **as a patient with normal hepatic function**, the following criteria must be met:

2. Negative result for serum hepatitis B surface antigen and hepatitis C antibody

3. Total bilirubin ≤1.5 x institutional upper limit of normal (ULN), albumin and prothrombin time within normal limits and must not have ascites (unless related to disease under study) or encephalopathy

4. Aspartate aminotransferase or serum glutamic oxaloacetic transaminase (AST), alanine aminotransferase or serum glutamic pyruvic transaminase (ALT) ≤2.5 x institutional ULN unless liver metastases are present in which case it must be ≤5 x ULN

All patients must fulfil the following criteria:

5. Provision of written informed consent prior to any study specific procedures.

6. Patients must be ≥18 years of age.

7. Histologically or, where appropriate, cytologically confirmed malignant solid tumour refractory or resistant to standard therapy or for which no suitable effective standard therapy exists. In case of HCC, histological or cytological confirmation is not required in the following situations, as per international guidelines of the scientific societies European Society for Medical Oncology (ESMO) and American Association for the Study of Liver Diseases (AASLD):

   – Nodules >2 cm with a typical feature of HCC on a dynamic imaging technique, or any nodule associated with α-fetoprotein (AFP) concentration >400 ng/ml or rising AFP on sequential determinations, do not require biopsy but should be considered as proven HCC (Jelic et al 2010).

   – Nodules >1 cm found on ultrasound screening of a cirrhotic liver should be investigated further with either 4-phase multi-detector CT scan or dynamic contrast enhanced MRI. If the appearances are typical of HCC (ie, hyper-vascular in the arterial phase with washout in the portal venous or delayed phase), the lesion should be treated as HCC. If the findings are not characteristic or the vascular profile is not typical, a second contrast-enhanced study with the other imaging modality should be performed, or the lesion should be biopsied (level II) (Bruix et al 2011).

8. Normal organ and bone marrow function measured within 28 days prior to administration of IP as defined below:

   - Haemoglobin ≥9.0 g/dL, with no blood transfusions in the previous 28 days
   - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
   - White blood cells (WBC) >3 x 10^9/L
   - Platelet count ≥75 x 10^9/L
   - Serum creatinine ≤1.5 x institutional ULN

9. Calculated serum creatinine clearance >50 mL/min (using Cockcroft-Gault formula or by 24-hour urine collection)

10. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.

11. Patients must have a life expectancy ≥8 weeks.

12. 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 of the first treatment period in Part A

    Postmenopausal is defined as:

    - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
    - Luteinising hormone and follicle-stimulating hormone levels in the postmenopausal range for women under 50 years of age
    - Radiation-induced oophorectomy with last menses >1 year ago
    - Chemotherapy-induced menopause with >1 year interval since last menses
    - Surgical sterilisation (bilateral oophorectomy or hysterectomy).

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

14. Patients must be on a stable concomitant medication regimen (with the exception of electrolyte supplements), 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

Patients 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, its agents and/or staff at the study site).

2. Previous enrolment in the present study.

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

4. Treatment in the previous 3 months before dosing in this study with any drug known to have a well defined potential for hepatoxicity (eg, halothane).

5. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 2 weeks prior to study treatment. The patient can receive a stable dose of bisphosphonates or denosumab for bone metastases before and during the study as long as these were started at least 4 weeks prior to treatment.

6. Patients who have received or are receiving inhibitors or inducers of CYP3A4 within the washout period (see Section 5.6 for guidelines and washout periods).

7. Toxicities (≥CTCAE Grade 2) caused by previous cancer therapy, excluding alopecia.

8. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. Patients with asymptomatic brain metastases or with symptomatic but stable brain metastases 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.

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

10. Patients considered a poor medical risk due to a serious uncontrolled medical disorder, non malignant systemic disease, uncontrolled seizures, 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, extensive bilateral interstitial lung disease on high resolution computer tomography (HRCT) scan, or any psychiatric disorder that prohibits obtaining informed consent.

11. Patients with a history of heart failure or left ventricular dysfunction.

12. Patients who have gastric, gastro-oesophageal or oesophageal cancer.

13. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders or significant gastrointestinal resection likely to interfere with the absorption of olaparib.

14. Breastfeeding women.

15. Immunocompromised patients eg, patients who are known to be serologically positive for human immunodeficiency virus (HIV).

16. Patients with a known hypersensitivity to olaparib or any of the excipients of the product.

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

18. Clinical judgment by the investigator that the patient should not participate in the study.

In addition to exclusion criteria 1 to 18, **patients with normal hepatic function** should not enter the study if the following exclusion criterion is fulfilled:

19. History or presence of hepatic disease known to interfere with the absorption, distribution, metabolism or excretion of olaparib.

In addition to exclusion criteria 1 to 18, **patients with mild or moderate hepatic impairment** should not enter the study if the following exclusion criteria are fulfilled:

20. Patients with hepatic encephalopathy (as described in the Child-Pugh Classification system, see Section 6.2.1.1).

21. Fluctuating or rapidly deteriorating hepatic function as indicated by widely varying or worsening of clinical and/or laboratory signs of hepatic impairment within the screening period (eg, advanced ascites, fever, active gastrointestinal bleeding).

22. Change in dose regimen of medically required medication within the last 2 weeks before screening and/or the use of disallowed co-medication in the 3 weeks prior to admission to the clinic.

23. Presence of acute liver disease caused by drug toxicity or by an infection.

24. Severe portal hypertension or surgical porto-systemic shunts.

25. Biliary obstruction or other causes of hepatic impairment not related to parenchymal disorder and/or disease of the liver.

26. Oesophageal variceal bleeding within the past 2 months.

27. Anticoagulant therapy with warfarin or related coumarins.

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions will apply to patients during both Part A and Part B of the study unless otherwise specified.

Contraception

Female patients of childbearing potential and their partners, who are sexually active, must agree to the use of 2 highly effective forms of contraception in combination throughout the period of taking study treatment and for at least 1 month after last dose of study drug. Male patients and their partners, who are sexually active and of childbearing potential, must agree to the use of 2 highly effective forms of contraception in combination, throughout the period of taking study treatment and for 3 months after last dose of study drug. Reliable methods of contraception should be used consistently and correctly; acceptable methods include barrier methods, implants, injectables, combined oral contraceptive methods, some IUDs, sexual abstinence or vasectomised partner. See Appendix F for details of acceptable birth control methods to be used within the study.

Concomitant medications

For restrictions regarding concomitant medications, please see Section 5.6.

Other restrictions

Patients will be required to fast for 4 hours prior to admission to the clinic at the screening visit.

In Part A, patients will be fasted from 1 hour before their olaparib dose until 2 hours after dosing. Water can be allowed as desired except for 1 hour before and after olaparib administration, excluding the water required to take the olaparib dose. In Part B, the olaparib may be taken with a light meal or snack.

In Part A, patients should not consume any grapefruit, grapefruit juice or grapefruit containing products from 48 hours before dosing until 96 hours post-dose.

5.2 Patient enrolment and initiation of investigational product

The PI will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Assign each potential patient a unique enrolment number code (E-code) beginning with 'E#' after written informed consent has been obtained. The E-code (EWWXYZZZ) will consist of a 2-digit country number (WW), the last digit of the study D code number (X), a 1-digit site number (Y), and a 3-digit serial number (ZZZ, starting with 001) issued by the study centre in order of informed consent taken.

3. Determine patient eligibility. See Sections 4.1 and 4.2

If a patient withdraws from participation in the study, then his/her enrolment/identification number cannot be reused.

If a patient discontinues their participation in the study, they cannot re-enter the study.

This is an open label study; patients will not be randomised.

Where possible, patients in each of the 3 groups will be matched for age and BMI, and selected so that there is an overall similar proportion of males and females (see Section 6.2.1.1).

Groups will be recruited so that, if possible, at least 3 patients of each sex are in each group. Patients with normal hepatic function and mild hepatic impairment will be recruited before those with moderate hepatic impairment. At least 3 months of safety data (and PK data if available) from at least 3 patients with mild hepatic impairment will be reviewed before recruiting patients with moderate hepatic impairment into the study, first in Part A and then in Part B. If the safety, tolerability and PK data from the 3 patients with mild hepatic impairment dosed continuously with olaparib for 3 months raises safety concerns for the continuous dosing of patients with moderate hepatic impairment, then patients with moderate hepatic impairment will not enter the study.

5.3 Procedures for handling patients incorrectly enrolled or initiated on investigational product

Patients 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 patients that do not meet the selection criteria are incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation (in either Part A or B), a discussion should occur between the AstraZeneca Physician or his/her representative and the investigator regarding whether to continue or discontinue the patient from treatment. Once a decision is made, investigators need to ensure they comply with all applicable requirements for human patient protection and ethical review.

The AstraZeneca Physician or his/her representative is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped and be withdrawn from the study.

5.4 Blinding and procedures for unblinding the study (Not applicable)

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 7.

Table 7 Identity of investigational product

Investigational product	Dosage form and strength
Olaparib	150 mg tablet
Olaparib	100 mg tablet[a]

[a] Used only in Part B in the event of dose reductions.

Full descriptive information for olaparib can be found in the IB.

For all centres, olaparib will be packed in high density polyethylene (HDPE) bottles with child resistant closures. In Part A of the study, patients will be dispensed the exact amount of olaparib for the dosing visit. In Part B of the study, the patients will be dispensed sufficient tablets for at least each cycle period, plus overage.

5.5.2 Doses and treatment regimens

5.5.2.1 Part A

For Part A of the study, each patient will receive a single dose of 300 mg olaparib (administered as 2 x 150 mg tablets). Patients will be fasted from 1 hour before their olaparib dose until 2 hours after dosing. Water can be allowed as desired except for 1 hour before and after olaparib administration. The olaparib will be administered orally with approximately 240 mL of water, with the patient in an upright position. The investigator or his/her delegate will administer the olaparib. The tablets should be swallowed whole and not chewed, crushed, or divided. If vomiting occurs after olaparib dosing, the dose should not be re-administered.

If a patient vomits within approximately 3 hours after dosing with olaparib, all PK sampling may be omitted but the safety assessments should continue as per the study schedule. The patient may proceed into Part B.

5.5.2.2 Part B (and continued use after end of Part B)

Patients who are eligible to continue in Part B will receive 300 mg bd oral olaparib (administered as 2 x 150 mg tablets) for the duration of their participation. Patients should aim to take their doses at similar times each day, approximately 12 hours apart. The olaparib should be swallowed whole with a glass of water, and not chewed, crushed, dissolved or divided. It may be taken with a light meal or snack.

5.5.3 Additional study drug (Not applicable)

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

The olaparib must be kept in a secure place under appropriate storage conditions and may only be dispensed by a pharmacist or a qualified designee. The IP label on the bottle specifies the appropriate storage.

5.6 Concomitant and post-study treatment(s)

5.6.1 Restrictions for patients with hepatic impairment

In Part A, patients with hepatic impairment are required to refrain from taking cholestyramine/colestipol and ranitidine/nizatidine within 10 hours before and 10 hours after dosing with olaparib.

5.6.2 Olaparib and CYP3A4

The use of any natural/herbal products or other traditional 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 in the case report form (CRF).

5.6.2.1 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 C_{max} 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 C_{max} 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 (eg, itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir and telaprevir) or inducers (eg, phenobarbitone, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) of these isozymes should be avoided with olaparib.

For patients taking strong inhibitors, the required washout period prior to starting olaparib is 2 weeks. For patients taking strong inducers, the required washout periods prior to starting olaparib in Part A are:

- Phenobarbitone, 5 weeks
- For any of the others, 4 weeks.

If the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare during Part B, the investigator must contact the AstraZeneca Physician or their designated Medical Monitor. 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 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. It is possible that olaparib may cause clinically relevant drug interactions with substrates of Pgp.

5.6.2.2 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 Pgp (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.

5.6.3 Other concomitant medications

Any medications, with the exceptions noted in Section 5.7 below, which are considered necessary for the patient's welfare, and which are believed will not interfere with the IP, may be given at the discretion of the investigator, providing the medications, the doses, dates, and reasons for administration are recorded in the CRF.

In addition, any unplanned diagnostic, therapeutic, or surgical procedure performed during the study period must be recorded in the comments section of the corresponding AE report.

Anticoagulant therapy: Patients with normal hepatic function who are taking warfarin may participate in this study; 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 for those patients with normal or impaired hepatic function.

Anti-emetics/anti-diarrhoeals: Prophylactic anti-emetics and/or anti-diarrhoeals will not be routinely given. Should a patient develop nausea, vomiting, and/or diarrhoea, which, in the investigator's opinion, is considered related to the IP, then appropriate treatment may be given.

Leukopenia and/or anaemia treatment: The use of colony-stimulating factors (CSFs) (eg, granulocyte-CSF [G-CSF], or granulocyte-macrophage CSF [GM-CSF]) should be managed as deemed appropriate by the investigator for the treatment of haematological AEs during Part B of the study (see Section 5.10).

The reason(s) for use, doses, and dates of treatment should be recorded in the patient's medical records and appropriate section of the CRF.

All medications (prescriptions or over-the-counter medications) present at the start of the study or started during the study or until 30 days from the end of the last protocol treatment and different from the IP must be documented in the CRF.

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 they cannot be managed with local or systemic analgesics and that the investigator does not feel that these are indicative of clinical disease progression during the study.

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.

5.6.5 Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on IP. Patients may continue the use of bisphosphonates or denosumab for bone

disease, and corticosteroids, provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning IP (see Section 4.1 and Section 4.2).

5.6.6 Live virus and bacterial vaccines

Live virus and bacterial vaccines should not be administered whilst the patient is receiving IP 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.

5.6.7 Medications that may NOT be administered

No other chemotherapy, immunotherapy, hormonal therapy (except hormone replacement therapy [HRT]), or other novel agent is to be permitted while the patient is receiving IP.

5.7 Treatment compliance

The administration of all medication (including IPs) should be recorded in the appropriate sections of the CRF.

For Part A, ie, when patients are at the study site, compliance will be assured by supervised administration of IP by the investigator or his/her delegate.

Patients will report any self-administered medications for the periods when they are not resident in the clinic.

For Part B, ie, when patients self-administer their olaparib, they should be given clear instructions on how and when to take their study treatment. Patients should aim to take their doses on outpatient days at similar times each day, approximately 12 hours apart. They should be instructed that the dose is to be swallowed whole with a glass of water and not chewed, crushed, dissolved or divided. It may be taken with a light meal or snack.

Patients will be issued with a Patient Diary Card, which contains clear instructions on how and when to take their study treatment, and the date of their next clinic appointment.

Study site pharmacy staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the CRF. 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 CRF. Patients must return all bottles and any remaining tablets when they discontinue IP.

5.7.1 Accountability

The IP 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 IPs, so as to ensure that:

Deliveries of such products from AstraZeneca or its representative 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 IP dispensed and returned.

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 IP was dispensed, the quantity and date of dispensing, and unused IP returned to the investigator. This record is in addition to any IP accountability information recorded on the CRF. 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. Dispensing and accountability records will continue to be collected after the end of Part B for as long as patients continue to receive IP.

5.8 Discontinuation of investigational product

Patients may be discontinued from IP and assessments at any time (applies to both Parts A and B). Specific reasons for discontinuing IP are:

- 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
- Worsened condition
- Disease progression
- The investigator believes they are no longer deriving clinical benefit (Part B).

5.8.1 Procedures for discontinuation of a patient from investigational product

If a patient discontinues IP during Part B, then they will attend a study treatment discontinuation visit and follow the procedures described in Table 6.

As described in Section 3.1, a patient may remain on study treatment after Part B if they and the investigator deem it appropriate. When the patient and the investigator decide to discontinue IP, the patient will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, he/she will be seen and assessed by an investigator(s). Adverse events will be followed up (see Sections 6.4.3 and 6.4.4), and IP should be returned to the site pharmacy.

Any patient discontinuing IP should be seen at 30 days (±7 days) after their last dose for the evaluations outlined in the study schedule. After discontinuation of IP, the PI/sub-investigator will perform the best possible observation(s), test(s), and evaluation(s), as well as give appropriate medication and all possible measures for the safety of the patient. In addition, they will record on the CRF the date of discontinuation, the reasons, manifestation, and treatment at the time of discontinuation. If patients discontinue IP, the AstraZeneca monitor or its representative must be informed immediately. Patients will be required to attend the treatment discontinuation visit (follow-up visit). The patient should return all IP.

After discontinuation of the IP at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease, or the patient is lost to follow up (see Sections 6.4.3 and 6.4.4). All new AEs and SAEs occurring during the 30 calendar days after the last dose of IP must be reported (if SAEs, they must be reported to AstraZeneca or its representative within 24 hours as described in Section 6.4.4) and followed to resolution as above. Patients should be contacted at least 30 days after discontinuing IP to collect and/or complete AE information and collect IP. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the IP should also be reported as an AE.

If a patient is withdrawn from the study, see Section 5.9.

5.9 Withdrawal from study

Patients are at any time free to withdraw from the study (IP 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 Sections 6.4.3 and 6.4.4) and questionnaires and IP 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
- Risk to patients as judged by the investigator and/or AstraZeneca or its representative

- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca or its representative
- Incorrectly enrolled patients, ie, the patient does not meet the required inclusion/exclusion criteria for the study
- The patient becomes pregnant
- Patient lost to follow-up.

5.10 Guidance for Investigators

The following text is guidance for investigators who treat patients with olaparib in Part B.

Where toxicity reoccurs following re-challenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then the patient may be considered for dose reduction or permanent discontinuation of treatment with olaparib.

Treatment may be interrupted if any CTCAE Grade 3 or 4 AE occurs that the investigator considers to be related to the administration of olaparib. Repeat dose interruptions can occur as needed for up to 2 weeks (14 days) on each occasion. If this has not resolved to at least CTCAE Grade 1 during the 2 weeks (14 days) dose interruption period, and/or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 200 mg bd), the patient should permanently discontinue treatment with olaparib. If toxicity is appropriately resolved, then the patient should resume treatment with olaparib, but with a dose reduction according to Table 8. If the event recurs with the same severity, treatment should be interrupted again and, on resolution, a further dose reduction made. If, on the re-starting treatment, the event continues to occur, the patient should permanently discontinue olaparib.

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

An exception to the management of olaparib-related toxicity is the occurrence of leukopenia and/or anaemia. In this case, the AE should be managed as deemed appropriate by the investigator (growth factor, transfusions), without interruption in IP or change in dose. However, growth factors should be discontinued once the AE has recovered to Grade 1 or better. They may be resumed, if necessary, if leukopenia/anaemia develops again and discontinued once it recovers.

The dose of olaparib must not be adjusted under any other circumstances unless the AstraZeneca Physician or representative gives prior agreement. Once the dose of olaparib has been reduced, under no account should it be re-escalated.

Olaparib should be discontinued for a minimum of 7 days before a patient undergoes therapeutic radiation treatment, or a minimum of 3 days for palliative radiation treatment (see Section 5.6.4).

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

Table 8 Dose reductions for olaparib in Part B only

Reduction	Dose level (tablets)
Initial dose level	300 mg bd (2 x 150 mg tablets)
1st Dose reduction due to CTCAE Grade 3 or 4 treatment-related SAE/AEs	250 mg bd (1 x 150 mg tablet and 1 x 100 mg tablet)
2nd Dose reduction due to CTCAE Grade 3 or 4 treatment related SAE/AEs	200 mg bd (2 x 100 mg tablets)

Management of anaemia

Adverse events of anaemia CTCAE Grade 1 or 2 (haemoglobin [Hb] ≥8 g/dL) should be managed as deemed appropriate by the investigator with or without interruption of study drug or change in dose. In some cases management of anaemia may require blood transfusions. However, if the patient develops anaemia CTCAE Grade 3 (Hb ≤8g/dL) or higher, study treatment should be interrupted for up to maximum of 4 weeks to allow for bone marrow recovery, and the patient should be managed appropriately. Study treatment can be restarted at the same dose if Hb has recovered to ≥9 g/dL. Any subsequent interruptions will require study treatment dose reductions.

If a patient has been treated for anaemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependant as judged by the 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 prolonged haematological toxicities while on study treatment

If the patient develops prolonged haematological toxicity such as:

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

Weekly differential blood counts including reticulocytes (calculate reticulocyte index, RI) and peripheral blood smear should be performed. If blood parameters remain clinically abnormal after 4 weeks of dose interruption or if more than one blood cell line is affected, the patient

should be referred to a haematologist for further investigations. Bone marrow analysis or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

Development of myelodysplastic syndrome should be reported as an SAE and full reports must be provided by the Investigator to AstraZeneca Patient Safety.

Management of neutropenia and leukopenia

Adverse events of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTCAE Grade 3 or higher neutropenia occurs. Primary prophylaxis with G-CSF is not recommended; however, if the 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 hours of the last dose of study treatment.

Study treatment can be restarted at the same dose if an AE of neutropenia or leukopenia have been recovered up to CTCAE Grade ≤1 (ANC >1.5 x 10^9/L). Any subsequent interruptions will require study treatment dose reductions.

Management of thrombocytopenia

An AE of thrombocytopenia should be managed as deemed appropriate by the investigator. If a patient develops thrombocytopenia CTCAE Grade 3 or higher study treatment should be interrupted for a maximum of 4 weeks. Any subsequent interruptions will require olaparib dose reductions. In some cases, management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality occurs, an interruption in study treatment dosing is recommended and a diagnostic workup (including a high resolution computed tomography [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.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The InForm 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 CRFs as specified in the study protocol and in accordance with the instructions provided.

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

6.2 Data collection at enrolment and follow-up

The study assessments are listed in the sections below and the timing of these assessments are detailed in Table 4 and Table 6.

It is important that PK sampling occurs as close as possible to the scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The sequence to be followed at a particular post-dose time point is:

1. Vital signs

2. PK blood sample (at scheduled time)

3. Any other assessments

For pre-dose assessments, vital signs, and PK samples should be collected within 60 minutes prior to dosing.

6.2.1 Screening

Before being entered into the study, patients will be assessed to ensure that eligibility criteria are met. Patients not meeting the criteria must not be entered into the study.

The following assessments and procedures should be performed within 28 days prior to first dose of IP:

- Signed informed consent for the study
- Date of birth, race, and ethnicity
- Classification of hepatic function (see Section 6.2.1.1)
- Menopausal status; serum or urine pregnancy test for women of childbearing potential (within 28 days prior to IP start and a confirmatory test before treatment at Visit 1)
- Medical and surgical history
- Germline BRCA status, if known
- Prior and concomitant medications including previous cancer therapies (if applicable)

- Physical examination, ECOG performance status, vital signs (supine BP and pulse, body temperature), ECG, body weight and height
- Haematology, clinical chemistry, serology (hepatitis B virus and hepatitis C virus) and urinalysis
- AEs must be captured from time of consent.

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

6.2.1.1 Classification of hepatic function

Patients will be classified as having normal hepatic function defined by the inclusion criteria for patients with normal hepatic function (see Section 4.1) or mild or moderate hepatic function as determined by the Child-Pugh Classification system as shown in Table 9, with the exception of hepatic encephalopathy (see exclusion criterion 20 in Section 4.2).

Child-Pugh A (mild impairment) = good operative risk = 5 to 6 points
Child-Pugh B (moderate impairment) = moderate operative risk = 7 to 9 points
Child-Pugh C (severe impairment) = severe operative risk = 10 to 15 points (not eligible for this study)

Table 9 Child-Pugh Classification System

	Points Scored for Observed Findings		
	1 point	**2 points**	**3 points**
Encephalopathy grade[a]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	<2	2 to 3	>3
Serum bilirubin (µmol/L	<34.2	34.2 – 51.3	>51.3
Serum albumin (g/dL)	>3.5	2.8 – 3.5	<2.8
Serum albumin (g/L)	>35	28 - 35	<28
Prothrombin time, sec prolonged	<4	4 to 6	>6
or			
INR	<1.16	1.16 – 1.56	>1.56

INR international normalised ratio; cps cycles per second
Table based on CHMP guidance: Committee for Medicinal Products for Human Use, 2005
[a]Encephalopathy
Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second (cps) waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behaviour, decerebrate, slow 2-3 cps delta activity

Where possible, patients in each of the 3 groups will be matched for age and BMI, and selected so that there is an overall similar proportion of males and females.

6.2.2 Follow-up procedures

A post-study medical examination will be performed at 30 days (±7 days) after the last dose of IP, regardless of during what part of the study the last dose was taken.

This will consist of:

- A physical examination (Part A follow-up only)
- Vital signs (including supine BP and pulse)
- Resting 12-lead ECG
- A blood sample for standard clinical chemistry and haematology assessments
- Mid-stream urine sample for urinalysis
- Recording of any AEs or concomitant medications.

6.2.3 Post study

After Part A of the study is completed, no further clinical data will be collected for this part of the study after the follow-up visit for patients who do not enter Part B. Patients will resume the regular follow-up schedule as suggested by their physician.

After Part B is completed (12 months from the date the last patient enters this part of the study), patients may continue to take olaparib (see Section 3.1). During this time, they will be seen as per their normal routine clinical schedule; it is recommended that patients are seen every 6 to 8 weeks. No clinical data will be collected other than SAEs.

Dispensing and accountability records will continue to be collected after the end of Part B for as long as patients continue to receive IP.

6.3 Efficacy (Not applicable)

6.4 Safety

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

6.4.1 Definition of adverse events

An AE 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, ECG). 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.

6.4.2 Definitions of serious adverse event

A SAE 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 patient 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.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse events (including SAEs) will be collected from the time of signed informed consent throughout the treatment period and up to and including the 30-day follow-up period in Part A. In Part B, AEs will be collected until 12 months after the last patient entered Part B, and including the 30-day follow-up period for any patients who discontinue. After the end of Part B, only SAEs will be collected.

Follow-up of unresolved adverse events

Any AEs/SAEs that are unresolved at the patient's last AE assessment (ie, 30-day follow-up visit in the study are followed up by the investigator for as long as medically indicated. AstraZeneca or its representative 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 (ie, 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. 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 IP, the investigator should notify AstraZeneca Patient Safety or its representative.

If patients who are gaining clinical benefit are allowed to continue IP following data cut off and/or post study completion then as a minimum all SAEs must continue to be collected and reported to Astra Zeneca Patient Safety or its representative within the usual timeframe (Section 6.4.4).

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- the date and time when the AE started and stopped
- the maximum CTCAE grade attained
- whether the AE is serious or not
- investigator causality rating against the IP (yes or no)
- action taken with regard to IP
- AE caused patient's withdrawal from IP (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 [reason]
- 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

The grading scales found in the revised National Cancer Institute CTCAE (NCI-CTCAE) v4.0 will be utilised for all events with an assigned CTCAE grading (CTCAE v4.0 2010). For those events without assigned CTCAE grades, the recommendation is the CTCAE criteria that convert mild, moderate, and severe events into CTCAE grades should be used.

A copy of the CTCAE version can be downloaded from the United States Department of Health and Human Services, National Institutes of Health, National Cancer Institute website (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

For each episode, the highest severity grade attained 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 6.4.2. 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 a 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 a SAE.

Causality collection

The Investigator will assess causal relationship between IP and each AE, 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?’

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

For a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel, "Have you had any health problems since the previous visit?" 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 (CSR). Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs and other safety variables 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 IP.

If deterioration in a laboratory value/vital sign/ECG is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign/ECG 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 patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix E '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 IP is being studied. It may be an increase in the severity of the disease under study and/or an increase in the symptoms of the disease. Expected progression of the patient's cancer and/or expected progression of signs and symptoms of the cancer, unless more severe in intensity or more frequent than expected for the patient's condition, should be considered as disease progression and not as an AE. Any events that 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 cancers) should be regarded as an AE and will generally meet at least 1 of the serious criteria (see Section 6.4.2). New primary cancers are those that are not the primary reason for the administration of the IP 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 condition for which the IP(s) is being used (advanced solid tumours), 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 IP 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 IP, must be reported as follows:

- Death that is clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the CRF but should not be reported as a SAE.

- Where death is not due (or not clearly due) to progression of the DUS, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 6.4.4 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 CRF'.

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

6.4.4 Reporting of serious adverse events

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

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 5 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.

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

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

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis parameters will be taken at the times given in the study plans (Table 4 and Table 6).

The following laboratory variables will be measured:

- Full haematology assessments for safety (Hb, red blood cells [RBC], platelets, mean corpuscular volume [MCV], mean corpuscular Hb concentration [MCHC], mean corpuscular Hb [MCH], WBC, differential white cell count and ANC should be performed in accordance with the study plans and when clinically indicated. Coagulation (aPTT and INR) will be performed at baseline and if clinically indicated. For patients taking warfarin reference Section 5.6.3.

- To investigate increases in MCV with olaparib treatment, additional haematology assessments of vitamin B12, folate, red blood cell folate and thyroid stimulating hormone (TSH) will be performed during Part B only. If available from the complete blood count report, the reticulocyte count and red cell distribution width should also be recorded. These additional assessments will be performed on Day 1, then monthly for the first 6 months, at discontinuation, and at the 30-day follow-up visit.

- Biochemistry assessments for safety (sodium, potassium, calcium, magnesium, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], AST, ALT, urea or blood urea nitrogen [BUN], total protein, albumin and lactate dehydrogenase [LDH]) will be performed.

- Urinalysis: protein, blood, glucose and bilirubin

In Part A, 2 pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential, one within 28 days prior to the start of IP and the other on Day 1 of the study prior to commencing treatment. In Part B, a pregnancy test will be conducted at baseline but should be repeated in the event of a suspected pregnancy during the study. Tests will be performed by the hospital's local laboratory. If results are positive, the patient is ineligible/must be discontinued from the study.

Routine urinalysis should be performed if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required. 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 CRF.

NB. In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix E '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.

6.4.6 Physical examination

Physical examinations will be conducted at the times specified in the study plans (Table 4 and Table 6). In addition, physical examinations will be conducted at each study visit during Part B, but will not be captured on the CRF. If new or aggravated physical findings imply deterioration compared with baseline, the finding should be reported as an AE.

Performance status will be assessed at screening and on Day 1 of Part B using the ECOG scale (see Appendix G).

6.4.7 Resting 12-lead ECG

Twelve-lead ECGs will be conducted at the times specified in the study plans (Table 4 and Table 6).

The ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. All 12-lead ECGs should be recorded while the patient is in the supine position. The investigator or designated physician will review the paper copies of each 12-lead ECG.

ECGs will be recorded at 25 mm/sec. 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 CRF. ECGs are required within 28 days prior to starting study treatment, at the final follow up visit, and when clinically indicated. A copy of the ECG indicating the study number, without patient identifiers, will be included in the patient's study file for monitoring by the study monitor.

6.4.8 Vital signs

Vital signs (including body temperature, where indicated) will be measured at the times specified in the study plans (Table 4 and Table 6). However, the investigator reserves the right to add extra assessments if there are any abnormal findings or for any other reason the investigator feels meets this requirement.

Supine BP and pulse will be measured using a semi-automatic BP recording device with an appropriate cuff size after the patient has been resting in bed for 10 minutes.

Deterioration as compared with baseline in protocol-mandated vital signs should only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP, or the investigator insists the abnormality should be reported as an AE.

Body temperature will be measured in degrees Celsius in accordance with local practice.

6.5 Pharmacokinetics

6.5.1 Collection of samples

Venous blood samples for determination of olaparib in plasma (4 mL), and for the measurement of protein binding (3 mL) will be taken at the time points detailed in Table 5. Although every attempt should be made to collect all samples as per protocol, it is accepted that this will not always be possible and therefore it is essential that the actual time and date of collection of each blood sample (whether collected as per protocol or not) is recorded in the CRF.

For blood volume see Section 7.1.

All biological samples will be collected, processed, labelled, and shipped for analysis as per the Laboratory Manual.

Results will only be reported for samples shipped within a timeframe for which the stability of olaparib in the samples has been validated and shown to be acceptable.

6.5.2 Determination of drug concentration

The plasma samples collected for protein binding determination will undergo equilibrium dialysis at Covance prior to the determination of concentrations of olaparib in the resulting plasma dialysate.

Samples for the determination of olaparib concentrations in plasma (total concentration) and plasma dialysate (free concentration) will be analysed by Covance on behalf of the Clinical Bioanalysis Alliance, AstraZeneca R&D using appropriate bioanalytical method(s). Full details of the bioanalytical method(s) used will be described in a separate bioanalytical report.

Results will only be reported for plasma samples shipped within a timeframe for which the stability of olaparib in the samples has been validated and shown to be acceptable.

Additional analyses may be conducted on the plasma samples to investigate reproducibility of incurred samples. Any results from these exploratory analyses will not be reported in the CSR but will be reported separately in a bioanalytical report.

6.6 Pharmacodynamics (Not applicable)

6.7 Pharmacogenetics (Not applicable)

6.8 Health economics (Not applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The maximum volume of blood that will be taken for any given patient for the purposes of the study will typically not exceed 215 mL.

The total volume of blood that will be drawn from each patient in this study is shown in Table 10.

Table 10 Volume of blood to be drawn from each patient: Parts A and B

Assessment		Sample volume (mL)	No. of samples A[a]	B[b]	Follow-up	Total volume (mL)
Safety	Clinical chemistry	2.7	3	12	0	**40.5**
	Clinical chemistry[c]	3.5	0	7	1	**28.0**
	Haematology	2.7	3	19	1	**62.1**
	RBC folate	2.0	0	7	1	**16.0**
Pharmacokinetic	Olaparib	4.0	15	0	0	**60.0**
	Olaparib protein binding	3.0	1	0	0	**3.0**
Total volume (mL)			**79.2**	**122.2**	**8.2**	**209.6**

[a] Includes screening/baseline blood volumes.
[b] Number of samples in Part B is based on a patient being in the study for an estimated maximum of 15 months.
[c] Includes TSH, vitamin B12 and folate (to be performed on Day 1, then monthly for the first 6 months, at discontinuation and at the 30-day follow-up visit.

Note: Table is for guidance. Exact blood volumes may differ depending on local requirements.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

7.2.1 Pharmacokinetic samples

Pharmacokinetic samples will be disposed of after finalisation of the Bioanalytical Report or 6 months after issuing the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK 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 CSR, but separately in a Bioanalytical Report.

7.3 Labelling and shipment of biohazard samples

The PI 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 'International Airline Transportation Association (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 patient unless agreed with AstraZeneca or its representative 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 PI keeps full traceability of collected biological samples from the patients while in storage at the study site 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.

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

7.5 Withdrawal of informed consent for donated biological samples

If a patient 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 patient is withdrawn from further study participation if consent is withdrawn.

The PI:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca or its representative
- Ensures that biological samples from that patient, 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 patient and AstraZeneca or its representative are informed about the sample disposal.

AstraZeneca or its representative ensures the central and bioanalytical laboratories holding the samples 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 International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient 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 (EC) 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 patients.

The investigator will ensure the distribution of these documents to the applicable EC and to the study site staff.

The opinion of the EC should be given in writing. The investigator should submit the written approval to AstraZeneca or its representative before enrolment of any patient into the study.

The EC should approve all advertising used to recruit patients for the study.

AstraZeneca or its representative 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 EC annually.

Before enrolment of any patient 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 or its representative will handle the distribution of any of these documents to the National Regulatory Authorities.

AstraZeneca or delegate will provide Regulatory Authorities, ECs and PIs with safety updates/reports according to local requirements.

AstraZeneca or its representative will be responsible for informing the Regulatory Authorities of SAEs/suspected unexpected serious adverse reactions (SUSARs) as per the European Union (EU) Clinical Trial Directive and/or local country regulations and guidelines.

8.4 Informed consent

The PI at each site will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient 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 patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an EC.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the co-ordinating 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 EC and if applicable, also the National Regulatory Authority, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca or its representative will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to EC see Section 8.3.

If a protocol amendment requires a change to a study site's Informed Consent Form, AstraZeneca and the study site's EC 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 EC.

8.6 Audits and inspections

Authorised representatives of AstraZeneca or its representative, a Regulatory Authority, or an EC may perform audits or inspections at the study site, 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, GCP guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca or its representative immediately if contacted by a regulatory agency about an inspection at the study site.

9. STUDY MANAGEMENT BY ASTRAZENECA

This study will be managed by Quintiles, on behalf of AstraZeneca, and Quintiles will act as the AstraZeneca representatives.

9.1 Pre-study activities

Before the first patient 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 patients 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 CSA between AstraZeneca and the investigator.

9.2 Training of study site personnel

Before the first patient 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 system(s) utilised.

The PI 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 PI 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 IP accountability checks are being performed

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

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

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

9.3.1 Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The PI at each study site should comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between the protocol and the CSA, the terms of this protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca or its representative and the PI should be in place before any study-related procedures can take place, or patients are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of Part A of this study is defined as either the 30-day follow-up date of the last patient to discontinue after Part A OR the date of the last patient in (LPI) into Part B, whichever is the later.

The end of Part B of this study is defined as the date when all patients receiving olaparib in Part B have been followed for a period of at least 12 months since the last patient entered Part B (defined as date of LPI in Part B plus 12 calendar months). 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 6.4.4 (Reporting of serious adverse events). In addition, as stated in Section 6.4.3 (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. After the end of Part B (when the clinical database is closed), investigators should complete paper SAE forms and fax them directly to the AstraZeneca Patient Safety Data Entry site for entering onto the AZ Patient Safety database.

Last subject last visit (LSLV) for the safety & tolerability objective is calculated as 12 months duration of treatment from the LPI (ie, LSLV = LPI + 12 months).

The study is expected to start in Q4 2013 with Part A to be completed in Q3 2016 and Part B to be completed in Q3 2017.

The study may be terminated at individual study sites 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.

The end of study is defined as 'the last visit of the last patient undergoing the study'.

10. DATA MANAGEMENT

Data management will be performed by Quintiles.

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 Quintiles.

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, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

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

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Other significant adverse event (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 DAEs (discontinuation of IP due to AE). Based on the expert's judgement, 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.

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 analysis of the plasma concentration data for olaparib will be done at AstraZeneca R&D. The actual sampling times will be used in the final PK parameter calculations, except for the pre-dose sample for which the time will be set to zero. All PK computations will be performed using Phoenix™ for WinNonlin.

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 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 the time of the last measurable concentration (AUC_{0-t}) calculated by linear up/log down trapezoidal summation
- 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: $AUC_{0-t} + C_{last}/\lambda_z$.

- Apparent plasma clearance (CL/F)
- Terminal half-life ($t_{½}$). Visual assessment will be used to identify the terminal linear phase of the concentration-time profile
- Apparent volume of distribution (V_z/F)
- Terminal rate constant (λ_z) estimated by log-linear least squares regression of the terminal part of the concentration-time curve
- Free C_{max} (C_{max} of unbound olaparib); calculated by multiplying total C_{max} value by estimated protein binding
- Free AUC (AUC of unbound olaparib); calculated by multiplying total AUC by estimated protein binding
- Unbound CL/F (CL/F of unbound olaparib); calculated from Dose/Free AUC.

Additional PK parameters may be determined if deemed appropriate.

11.3 Calculation or derivation of efficacy variable(s) (Not applicable)

11.4 Calculation or derivation of patient reported outcome variables (Not applicable)

11.5 Calculation or derivation of pharmacodynamic variables(s) (Not applicable)

11.6 Calculation or derivation of pharmacogenetic variables (Not applicable)

11.7 Calculation or derivation of health economic variables (Not applicable)

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

12.1 Description of analysis sets

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

The analysis sets are defined in Table 11.

Table 11 Definition of analysis sets

Analysis Set	Population
PK analysis set	All patients who receive an olaparib dose and have full PK sampling up to 96 hours post-dose.
Evaluable for Safety	All patients who receive at least 1 dose of olaparib and for whom any post-dose data are available will be included in the safety population

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

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 time frame 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 Quintiles under the direction of the Biostatistics Group, AstraZeneca using SAS® version 8.1 or higher and, where appropriate, additional validated software.

A comprehensive Statistical Analysis Plan (SAP) will be prepared 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 Evaluable for Safety analysis set will be summarised. Demographic and baseline characteristics will be summarised and listed for the Evaluable for 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

Part A

The database will be locked once all patients in the mild hepatic impairment and normal hepatic function groups have completed Part A. An interim analysis will be performed to compare the PK, safety and tolerability of olaparib in subjects enrolled in these 2 groups. The interim analysis will be reported in a full CSR.

Subsequently, after the last patient has completed Part A (including patients in the moderate hepatic impairment group), the database for Part A of the study will be locked and the data will be reported in a further CSR.

Part B

On completion of Part B, a further database lock will occur and the Part B data will be reported in a CSR addendum.

12.2.2 Pharmacokinetics (Part A only)

The sample bioanalysis will be performed by Covance. The merging of PK concentration data with actual PK sampling times will be performed by Quintiles Data Management. 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 Quintiles 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, minimum and maximum values.

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. Ratios and any corresponding confidence intervals (CIs) that are obtained during inferential statistical analysis shall be reported as a percent with 2 decimal places (eg, 99.88).

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 hepatic function group (moderate hepatic impairment, mild hepatic impairment or normal hepatic function.

The goal of the statistical analysis in Part A is to estimate the effect of hepatic function on the PK of olaparib. Following log-transformation, C_{max} and AUC (or $AUC_{0\text{-}t}$, if AUC is not adequately estimable) of olaparib will be separately analysed by analysis of variance (ANOVA), fitting a term for hepatic function group (moderate hepatic impairment, mild hepatic impairment or normal hepatic function).

The analysis will be carried out to compare the ratio of geometric means (gmeans) of the following groups:

1. Child-Pugh A classified patients (mild hepatic impairment) compared to patients with normal hepatic function (controls).

2. Child-Pugh B classified patients (moderate hepatic impairment) compared to patients with normal hepatic function (controls).

The results of these analyses will be presented in terms of geometric means for each hepatic function group. The ratio of geometric means of each hepatically impaired group compared to the normal group (mild/moderate: controls) will be presented with the respective 1-sided 95% upper confidence limit.

The possibility that hepatic impairment has a clinically relevant effect on the exposure of olaparib will be considered if the upper 1-sided 95% confidence limit for the ratio does not lie below the limit of 2, where the limit of 2 implies a doubling in exposure.

Assumptions of normality and constancy of variance will be explored in all analyses and, where necessary, an appropriate transformation (eg. rank) or non-parametric technique (eg. Mann-Whitney test) will be used to validate the results of the main analysis.

An interim analysis will be performed once all patients in the normal hepatic function and mild hepatic impairment groups have completed Part A. The interim PK analysis will be as described above, but limited to a comparison between the normal hepatic function and mild hepatic impairment groups. For details of the interim analysis, see Section 12.2.4.

12.2.3 Safety (Part A and Part B)

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 examination.

Appropriate summaries of AEs, laboratory data, and vital signs will be produced. AEs will be summarised separately for Parts A and B of the study. Laboratory data, vital signs, physical examination, body temperature and ECG will be summarised by hepatic function group (moderate hepatic impairment, mild hepatic impairment or normal hepatic function) and by study day. 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 IP.

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]). Adverse events reported before administration of olaparib will be listed only and be referred to as "pre-treatment." Treatment emergence will be defined for each part of the study (A and B).

For Part A, a treatment emergent AE (TEAE) will be defined as an AE with the start date and time on or after the first dose date and time, and up to (not including) the date and time of the first dose in Part B, or up to (and including) 30 days after dosing in Part A.

For Part B, a TEAE will be defined as an AE with the start date and time on or after the first dose date and time in Part B, and up to (and including) 30 days after the last dose date in the study.

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 by part, 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 for 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.

12.2.4 Interim analysis

An interim analysis will be performed to compare the PK, safety and tolerability of olaparib in subjects with mild hepatic impairment to those with normal hepatic function. Any patients enrolled into the moderate hepatic impairment group at the time of data-cut off for this interim analysis will be listed but not summarised.

The data will be displayed, in both the tables and listings, by hepatic group and will include a total column for an overall summary. Summary tables will display mild hepatic impairment and normal hepatic function while listings will also display the moderate hepatic impairment group.

The PK analyses performed during the interim analysis will compare the normal hepatic function and mild hepatic impairment groups only, but will otherwise be the same as those described for the final analysis of Part A data in Section 12.2.2.

12.3 Determination of sample size

The study has been sized to provide adequate PK information to assess the effects of hepatic impairment on the PK of olaparib, whilst exposing as few patients as possible to the IP and procedures. Based on the estimate of between-patient standard deviation (SD) for log AUC from Study D0810C00024 of 0.531, including 8 patients per arm provides approximately 80% chance that a 1-sided 95% confidence interval would exclude the possibility of a doubling in AUC.

Approximately 30 patients with advanced solid tumours will be entered to ensure that at least 24 evaluable patients complete the study (8 patients with normal hepatic function, 8 with mild hepatic impairment [Child-Pugh A] and 8 with moderate hepatic impairment [Child-Pugh B]). An evaluable patient is defined as a patient having full PK sampling to 96 hours post dose of olaparib.

12.4 Data monitoring committee (Not applicable)

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The PI 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 6.4.4.**

In the end of a medical emergency the Investigator may contact the 24-hour Quintiles Medical Emergency Contact Centre [redacted]

13.2 Overdose

There is currently no specific treatment in the event of overdose of olaparib and possible symptoms of overdose are not established.

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- 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 IP occurs in the course of the study, then investigators or other study site personnel should 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 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca or its representative.

13.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study, olaparib should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP 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 patient 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 6.4.4, and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

13.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose.

Pregnancy of the patient's partner 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 3 months after the last dose should be followed up and documented.

14. LIST OF REFERENCES

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Clinical Study Protocol Appendix B	
Drug Substance	Olaparib (AZD2281, KU-0059436)
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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	
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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.

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Clinical Study Protocol Appendix D	
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Appendix D
Pharmacogenetics Research (Not Applicable)

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Clinical Study Protocol Appendix E	
Drug Substance	Olaparib (AZD2281, KU-0059436)
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Appendix E
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:

- 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:

- 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 were 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 (NOT APPLICABLE)

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?

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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Revised Clinical Study Protocol Appendix F	
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Appendix F
Acceptable Birth Control Methods

1. 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 2 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 2 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 for women of childbearing potential and their partners and for 3 months after last dose for male patients. Periodic abstinence (eg, 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 (eg, 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 (eg, EE and etonogestrel) PLUS male condom

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Clinical Study Protocol Appendix G	
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Appendix G
Eastern Cooperative Oncology Group (ECOG) Performance Status

1. ECOG PERFORMANCE STATUS

Patient ability	**Score**
Fully active, able to carry on all pre-disease performance without restriction	**0**
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	**1**
Ambulatory and capable of all self-care, but unable to work. Up and about more than 50% of waking hours	**2**
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	**3**
Completely disabled, unable to carry out any self-care and confined totally to bed or chair	**4**