Clinical Study Protocol

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0816C00004
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A Randomised, Open-label, Three-part, Phase I Study to Determine the Effect of Food on the Pharmacokinetics of Olaparib and to Provide Data on the Effect of Olaparib on QT Interval Following Oral Dosing of a Tablet Formulation in Patients with Advanced Solid Tumours

Sponsor: AstraZeneca [redacted]

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

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AstraZeneca

PROTOCOL SYNOPSIS

A Randomised, Open-label, Three-part, Phase I Study to Determine the Effect of Food on the Pharmacokinetics of Olaparib and to Provide Data on the Effect of Olaparib on QT Interval Following Oral Dosing of a Tablet Formulation in Patients with Advanced Solid Tumours

International Co-ordinating Investigator or Principal Investigator or National Co-ordinating Investigator

[redacted]

Study centre(s) and number of patients planned

This study will be conducted at approximately 8 sites in Western Europe, with approximately 48 patients enrolled and at least 42 evaluable patients required.

Study period		Phase of development
Estimated date of first patient enrolled	[redacted]	Clinical pharmacology (I)
Estimated date of last patient completed (Part A)	[redacted]	
Estimated date of last patient completed (Part B)	[redacted]	
Estimated data of last patient completed (Part C)	[redacted]	

Objectives

The primary objective of this study is to investigate the effect of food on the pharmacokinetics (PK) of olaparib following oral dosing of the tablet formulation in patients with advanced solid tumours.

The secondary objectives are to investigate the effect of olaparib on the QT interval corrected for heart rate (QTc) following single (Part A) and multiple (Part B) oral doses of the tablet formulation, and to investigate further the safety and tolerability of olaparib following oral dosing of the tablet formulation in patients with advanced solid tumours.

Study design

This is a 3-part study in patients with advanced solid tumours: Part A will determine the effect of food on the pharmacokinetics of olaparib and the effect of olaparib on QT interval following a single oral dose of olaparib tablets; Part B will determine the effect of olaparib on the QT interval following multiple oral dosing of olaparib tablets; Part C will allow patients

continued access to olaparib tablets after PK and QT phases and will provide for additional safety data collection. A total of 48 patients are planned to be enrolled, with at least 42 evaluable patients required to complete the study.

Part A of this study is a randomised, open-label, 2-treatment period crossover design. Each patient will receive a single oral dose of olaparib tablets 300 mg in each of 2 treatment periods (once in the overnight fasted state and once immediately following a high-fat meal), with at least 5 and no more than 14 days (washout) between doses. Digital electrocardiogram (dECG), PK assessments, and safety assessments will be obtained for up to 72 hours post-dose in each treatment period. Additionally, during the first treatment period, patients will undergo baseline dECG assessments on Day -1 (ie, the day prior to dosing) at clock times matched to planned/scheduled dECG assessment times on the dosing day (Day 1). Patients will check into the clinic on the evening of Day -2 (first treatment period) or on the evening of Day -1 (second treatment period) and remain resident until 24 hours after each dose of olaparib tablets. The dECGs performed on Day 1 of each treatment period will be clock-time matched to the actual times that the Day -1 dECGs are performed in the first treatment period. Patients will return to the clinic for assessments on Days 3 and 4 of each treatment period. On Day 1 of Part A patients should be fasted over the same time period as Day -1.

Part B is an open-label study in the same patients who participated in Part A. Upon completion of Part A, providing the patient continues to meet the study inclusion and exclusion criteria and, following a washout period of at least 5 days and no more than 14 days between the last dose in Part A and Day -1 of Part B, each patient will receive olaparib tablets 300 mg twice daily (bd) for 5 days. Patients will check into the clinic in the evening of Day -2. On Day -1, baseline dECG assessments will be performed at clock times matched to planned/scheduled dECG assessment times on Day 5. Patients will be discharged from the clinic on the evening of Day -1. Patients will self-administer their olaparib doses under fasted conditions (from 1 hour prior to 2 hours after dosing) from Day 1 up to the morning of Day 4 on an outpatient basis. On the evening of Day 4, patients will check back into the clinic, and will receive their Day 4 evening dose. On the morning of Day 5, patients will receive their Day 5 morning dose after an overnight fast and will remain fasting for 4 hours post-dose. Patients will undergo dECG and PK assessments pre-dose and for 12 hours post-dose. The dECGs performed on Day 5 will be clock-time matched to the actual times that the Day -1 dECGs are performed. Patients will be discharged from the clinic after completing 12-hour assessments on Day 5, and will self-administer their evening Day 5 dose of olaparib tablets. On Day 5 of Part B patients should be fasted over the same time period as Day -1.

In both Parts A and B, patients are allowed to undergo the Day -1 (baseline) dECG evaluations on Day -2 or Day -3, if necessary, as long as the washout period by the start of baseline procedures for Part B has been at least 5 days since the previous treatment. If baseline assessments are done earlier than Day -1, then the periods of in-house confinement will be adjusted accordingly. For example, if baseline assessments are on Day -3, then patients will check into the clinic in the evening of Day -4 and will leave the clinic the morning of Day -2 after the 24-hour dECG measurement for Part A or the evening of Day -3

after the 12-hour dECG measurement for Part B. Patients will check back into the clinic in the evening of Day -1.

On completion of Part B, patients may be entered into Part C and continue to take olaparib tablets (300 mg bd) if they and the investigator agree that this is appropriate. Patients should start Part C immediately after the last dose received in Part B. Patients will have weekly clinic visits for the first 4 weeks; thereafter visits will be every 4 weeks. Part C will be of 12 months' duration from the date the last patient enters this part of the study.

During and after Part C, patients may continue to take olaparib tablets, 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 the olaparib tablets for any other reason. After the end of Part C (12 months after the last patient entered Part C), patients will be seen as per their normal routine clinical schedule and no clinical data will be collected, other than serious adverse events (SAEs) and drug dispensing/accountability.

Patients will return to the clinic for follow-up assessments 30 days (±7 days) after their last dose (regardless of whether the last dose was in Part A, Part B, Part C, or the continued access phase after Part C). If a patient discontinues olaparib tablets during Part C, 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 and are able to eat a high-fat meal will be recruited.

Investigational product, dosage and mode of administration

In Part A, each patient will receive a single 300 mg oral dose of olaparib, given as the tablet formulation, in each of 2 treatment periods (once in the overnight fasted state and once immediately following a high-fat meal). Each dose will comprise 2 x 150 mg tablets for oral administration.

In Part B, each patient will receive 5 days of olaparib treatment at 300 mg bd, given as the tablet formulation, under fasted conditions (no food from 10 hours prior to 4 hours after the Day -1 and Day 5 morning olaparib doses and from 1 hour prior to 2 hours after the other olaparib doses). Each dose will comprise 2 x 150 mg tablets for oral administration taken bd, approximately 12 hours apart, at the same time in the morning and the evening.

In Part C, patients will receive 300 mg oral olaparib bd, given as the tablet formulation, for the duration of their participation.

Comparator, dosage and mode of administration

None.

Duration of treatment

For Part A, patients will each receive 2 single doses of olaparib 300 mg (tablet formulation) over a period of 5 to 14 days.

For Part B, patients will each receive 10 doses of olaparib 300 mg (tablet formulation) over a period of 5 days (300 mg bd for 5 days).

Patients participating in Part C will receive continuous dosing of olaparib 300 mg bd (tablet formulation).

Outcome variables:

- Pharmacokinetics

  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 measurable time point (AUC_{0-t}), area under the plasma concentration-time curve from zero to infinity (AUC), apparent clearance following oral administration (CL/F), apparent volume of distribution (V_z/F), terminal rate constant (λ_z), and terminal half-life ($t_{1/2}$). Other parameters may be determined if deemed appropriate.

  In Part B, the following variables will be calculated for olaparib where the data allow: C_{max}, t_{max}, minimum plasma concentration (C_{min}), time to reach minimum plasma concentration (t_{min}), area under the plasma concentration-time curve over the dosing interval ($AUC_{0-\tau}$), average concentration over the dosing interval (C_{avg}), fluctuation index (FI), and CL/F. Other parameters may be determined if deemed appropriate.

  Pharmacokinetics will not be measured in Part C.

- Pharmacodynamics

  Digital ECGs will be recorded at baseline (Day -1) during Part A (first treatment period only) and Part B and then at specific time points pre-dose and following each dose in Part A and on Day 5 of Part B. Measurement times on Day -1 of Part A and Part B will be clock-time matched to planned/scheduled measurements on Day 1 of Part A and on Day 5 of Part B, respectively. The dECGs taken on Day 1 of Part A and Day 5 of Part B will be clock-time matched to the actual measurements taken on Day -1 of Part A (first treatment period) and Part B, respectively. Electrocardiogram (ECG) intervals including QT uncorrected for heart rate as well as QTc using Fridericia's, Bazett's, and study-specific corrections will be determined (triplicates at each time point) and summarised. Heart rate data and RR interval (the time between 2 successive heart beats) will also be summarised.

  Pharmacodynamics (PD) will not be measured in Part C.

- Safety

  Assessment of adverse events (AEs) graded by Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (CTCAE v4.03 2010), physical examination, vital signs (including blood pressure, pulse), standard 12 lead ECGs, and evaluation of laboratory parameters (clinical chemistry, haematology, and urinalysis).

Statistical methods

The primary objective of this study is to investigate the effect of food on the PK of olaparib given as the tablet formulation. The study has been sized to provide an estimate of the difference between olaparib PK parameters in the fed and fasted states. Based on the estimate of within-patient standard deviation (SD) for log AUC from Studies D0180C00002 and D0180C00003 of 0.26, and assuming a true food effect difference of 5%, 42 evaluable patients (21 per-sequence) will give 90% power of showing that the 90% confidence interval (CI) for the food effect (ratio of geometric least-squares means of AUC or C_{max} in the fed state to the fasted state) lies entirely within the range of 0.8 and 1.25. A total of 48 patients will be entered to ensure that at least 42 evaluable patients complete the study. nQuery v7.2 was used for the sample size calculations.

The goal of the statistical analysis is to estimate the effect of food on the PK of olaparib given as the tablet formulation. Following log-transformation, C_{max} and AUC (or AUC_{0-t}, if AUC is not adequately estimable) of olaparib will be separately analysed by mixed-effect analysis of variance (ANOVA), fitting terms for treatment (food condition: fasted or high-fat meal), sequence, and treatment period. Patient within sequence will be treated as a random effect in the model. Point estimates and adjusted 90% CIs for the difference in treatment (fasted or high-fat meal) will be constructed. The point estimate and adjusted 90% CIs will then be exponentially back transformed to provide point and CI estimates for the ratio of interest (ie, C_{max} or AUC of olaparib for the high-fat meal to C_{max} or AUC of olaparib in the fasted state). No food effect on the PK of olaparib will be concluded if the 2-sided 90% CIs for the ratios of AUC (or AUC_{0-t} as previously noted) and C_{max} are within the range of 0.80 to 1.25.

An analysis of t_{max} using the Wilcoxon Signed Rank Test, and the Lehman median estimator of difference (fed-fasted) and 90% CIs will also be presented.

The PD (dECG) data will be listed and summarised using descriptive statistics. Additionally dECG data from this study will be pooled with data from another study (AstraZeneca Study D0816C00007) and analysed using statistical methods and PK/PD modeling. The methodology for these analyses will be described in a separate QT analysis plan.

Safety data will be listed and summarised using descriptive statistics.

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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
ADP	Adenosine diphosphate
AE	Adverse event (see definition in Section 6.3.1)
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
$AUC_{0-\tau}$	Area under plasma concentration-time curve over the dosing interval, τ
bd	Twice daily (Latin: *bis die*)
BP	Blood pressure
BRCA	Breast cancer gene
BUN	Blood urea nitrogen
C_{avg}	Average plasma drug concentration over the dosing interval
CHO	Chinese hamster ovary
CI	Confidence interval
C_{last}	Last quantifiable concentration
CL/F	Apparent plasma clearance following oral administration
Clock-matched time	A clock time on one day corresponding to the same clock time on another day
C_{max}	Maximum plasma drug concentration
C_{min}	Minimum plasma drug concentration
CRF	Case Report Form
CRO	Contract research organization
CSA	Clinical Study Agreement
CSF	Colony-stimulating factor

Abbreviation or special term	Explanation
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DCIS	Ductal carcinoma in situ
dECG	Digital electrocardiogram
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
DSB	Double-strand break
E-code	Enrolment code
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EU	European Union
FDA	(United States) Food and Drug Administration
FI	Fluctuation index
G-CSF	Granulocyte-CSF
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GM-CSF	Granulocyte-macrophage CSF
GMP	Good Manufacturing Practice
Hb	Haemoglobin
hERG	Human Ether-a-go-go Related Gene
HIV	Human immunodeficiency virus
HR	Homologous recombination repair
HRCT	High resolution computed tomography
HRD	Homologous recombination repair deficiencies
HRT	Hormone replacement therapy
IB	Investigator's Brochure
IC50	50% inhibitory concentration
ICH	International Conference on Harmonisation
INR	International normalised ratio

Abbreviation or special term	Explanation
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
IUD	Intrauterine device
LDH	Lactate dehydrogenase
LOQ	Limit of quantification
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
NQ	Non-quantifiable
OAE	Other Significant Adverse Event (see definition in Section 11.1.1)
PARP	Polyadenosine 5'-diphosphoribose polymerase
PD	Pharmacodynamics
%CV	Percent coefficient of variation
%GCV	Geometric %CV
PI	Principal Investigator
PK	Pharmacokinetics
PQ	PQ interval of ECG
PR	PR interval of ECG
QRS	QRS interval of ECG
QT	QT interval of ECG
QTc	QT interval corrected for heart rate
QTcB	QT interval (corrected for heart rate using Bazett's correction)
QTcF	QT interval (corrected for heart rate using Fridericia's correction)
QTcI	QT interval (corrected for heart rate using individual-specific correction)
RBC	Red blood cells
RR	RR interval of ECG
SAE	Serious adverse event (see definition in Section 6.3.2).

Abbreviation or special term	Explanation
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SSB	Single-strand break
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach maximum plasma concentration
t_{min}	Time to reach minimum plasma concentration
TP 1	Treatment period 1
TP 2	Treatment period 2
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 (HR). Tumours with HR 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 is considered 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.

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.

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 $t_{1\backslash 2}$, 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 (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.

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 profile of olaparib when administered immediately following a high-fat meal when compared with administration in the fasted state.

Olaparib does not produce any clinically significant changes in the QT interval or QT interval corrected for heart rate (QTc) following either single or multiple dosing.

Olaparib demonstrates an acceptable safety profile in patients with advanced solid tumours.

1.3 Rationale for conducting this study

Part A of this study is an investigation of the effect of food on the PK of olaparib given as the tablet formulation. There are currently no robust clinical data on the effect of food on the PK of olaparib. Therefore it is anticipated that the results from this study will help to define what, if any, drug administration guidance related to food intake is needed for future/ongoing studies with olaparib.

Part A is a 2-period crossover design to allow the investigation of the effect of food within each patient and in a randomised manner. The study will be conducted using the Food and Drug Administration (FDA) standard high-fat meal. If no effect is seen with the high-fat meal, then this will indicate that no food restrictions need to be applied.

Cancer patients are required for this study as pre-clinical toxicology data preclude the use of olaparib in healthy volunteers. 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.

Both Parts A and B are an investigation of the effect of olaparib, given as the tablet formulation, on the QT interval. There are currently limited clinical data on the effect of olaparib on the QT interval. The pre clinical work showed no effect in dogs and the human Ether-a-go-go Related Gene (hERG) assay showed a 50% inhibitory concentration (IC50) of 226 μM, approximately 25-fold greater than the highest maximum steady-state unbound plasma concentration of olaparib achieved following a 400 mg bd tablet dose (9.2 μM). There were also no significant cardiology findings in the standard anaesthetised dog model.

There are limitations extrapolating pre-clinical data to the clinical setting, and there are limited clinical cardiology data. In order to address the need for data to assess cardiovascular risk, detailed monitoring conducted in the appropriate patient setting has been built into this study. Therefore, Parts A and B of this study will involve digital ECG (dECG) monitoring at specific pre defined time points, and will provide QTc data post single and post multiple dosing of olaparib tablets. Part B has been designed as a non-randomised sequential part of the overall study that patients can enter directly on completing Part A.

Part C will allow patients who have participated in Parts A and B, and received up to 12 oral doses of olaparib tablets, to receive a therapeutic dose of olaparib tablets on a continuous basis and therefore possibly gain clinical benefit. Safety and tolerability data collected in Part C will add to the safety database for patients with advanced solid malignancies treated with oral olaparib tablets.

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 considers that olaparib continues to demonstrate an overall acceptable 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 AE, vital sign, 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 or Part B of the study due to the short dosing periods, some benefit may be gained in Part C. If the investigator believes it is in the patient's interest, the patient may continue treatment with olaparib tablets until such time as their disease progresses, the investigator believes they are no longer deriving clinical benefit, or they stop taking the olaparib tablets for any other reason.

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 tablets in patients is acceptable.

2. STUDY OBJECTIVES

2.1 Primary objective

Table 1 Primary objective

Primary objective	Primary outcome variable(s)
To investigate the effect of food on the pharmacokinetics (PK) of olaparib following oral dosing of the tablet formulation in patients with advanced solid tumours	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 measurable time point (AUC_{0-t}), area under the plasma concentration time curve from zero to infinity (AUC), apparent clearance following oral administration (CL/F), apparent volume of distribution (V_z/F), terminal rate constant (λ_z), and terminal half-life ($t_{1/2}$). Other parameters may be determined if deemed appropriate.

2.2 Secondary objectives

Table 2 Secondary objectives

Secondary objectives	Secondary outcome variables
To investigate the effect of olaparib on the QT interval following oral dosing of the tablet formulation in patients with advanced solid tumours	ECG intervals (including QT and QTc interval)
To assess the safety and tolerability of olaparib following oral dosing of the tablet formulation in patients with advanced solid tumours	Assessment of AEs, graded by CTCAE (v4.03), physical examination (including BP and pulse), and evaluation of laboratory parameters (clinical chemistry, haematology, and urinalysis)

AE adverse event; BP blood pressure; CTCAE Common Terminology Criteria for Adverse Event; ECG electrocardiogram

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 3-part study in patients with advanced solid tumours: Part A will determine the effect of food on the pharmacokinetics of olaparib and the effect of olaparib on QT interval following a single oral dose of olaparib tablets; Part B will determine the effect of olaparib on the QT interval following multiple oral dosing of olaparib tablets; Part C will allow patients continued access to olaparib tablets after PK and QT phases and will provide for additional safety data collection. A total of 48 patients are planned to be enrolled at approximately 8 sites in Western Europe; approximately 42 evaluable patients will be expected to complete the study.

Part A of this study is a randomised, open-label, 2-treatment period crossover study in approximately 48 patients with advanced solid tumours. Each patient will receive a single oral dose of olaparib tablets 300 mg in each of 2 treatment periods (once in the overnight fasted state and once immediately following a high-fat meal at breakfast time), with at least 5 and no more than 14 days (washout) between doses. Digital ECG, PK assessments, and safety assessments will be obtained for up to 72 hours post-dose in each treatment period. Additionally, during the first treatment period, patients will undergo baseline dECG assessments on Day -1 (ie, the day prior to dosing) at clock times matched to planned/scheduled dECG assessment times on the dosing day (Day 1). Patients will check

into the clinic on the evening of Day -2 (first treatment period) or the evening of Day -1 (second treatment period) and remain resident until 24 hours after each dose of olaparib tablets (Day 2). The dECGs performed on Day 1 in each treatment period will be clock-matched to the actual times that the Day -1 dECGs are performed in the first treatment period. Patients will return to the clinic for assessments on Days 3 and 4 of each treatment period. On Day 1 of Part A patients should be fasted over the same time period as Day -1.

The overall study plan for Part A of the study is provided in Table 3. Pharmacokinetic sampling and dECG measurements in Part A will be conducted as shown in Table 6.

Part B of this study is an open-label study in the same patients who participated in Part A. Upon completion of Part A, following a washout period (of at least 5 days and no more than 14 days between the last dose in Part A and Day -1 of Part B) and providing the patient continues to meet the study inclusion and exclusion criteria, each patient will receive olaparib tablets 300 mg bd for 5 days. For the morning dose on Day 5 of this part of the study, patients will undergo dECG and PK assessments pre-dose and for 12 hours post-dose. Patients will check into the clinic on the evening of Day -2. On Day -1, baseline dECG assessments will be performed at clock times matched to planned/scheduled dECG assessment times on Day 5. Patients will be discharged from the clinic on the evening of Day -1. Patients will self-administer their olaparib doses under fasted conditions (from 1 hour prior to 2 hours after the olaparib dose) from Day 1 up to the morning of Day 4 on an outpatient basis. On the evening of Day 4, patients will check back into the clinic, and will receive their Day 4 evening dose. On the morning of Day 5, patients will receive their Day 5 morning dose after an overnight fast and will remain fasting for 4 hours post-dose. Patients will undergo dECG and PK assessments pre-dose and for 12 hours post-dose. The dECGs performed on Day 5 will be clock-matched to the actual times that the Day -1 dECGs are performed. Patients will be discharged from the clinic after completing 12-hour assessments on Day 5, and will self-administer their evening Day 5 dose of olaparib tablets. On Day 5 of Part B patients should be fasted over the same time period as Day -1.

The overall study plan for Part B of the study is provided in Table 4. Pharmacokinetic sampling and dECG measurements in Part B will be conducted as shown in Table 7.

In both Parts A and B, patients are allowed to undergo the Day -1 (baseline) dECG evaluations-on Day -2 or Day -3, if necessary, as long as the washout period by the start of baseline procedures for Part B has been at least 5 days since the previous treatment. If baseline assessments are done earlier than Day -1, then the periods of in-house confinement will be adjusted accordingly. For example, if baseline assessments are on Day -3, then patients will check into the clinic in the evening of Day -4 and will leave the clinic the morning of Day -2 after the 24-hour dECG measurement for Part A or the evening of Day -3 after the 12-hour dECG measurement for Part B. Patients will check back into the clinic in the evening of Day -1.

On completion of Part B, patients may be entered into Part C and continue to take olaparib tablets (300 mg bd) if they and the investigator agree that this is appropriate.

Patients should start Part C immediately after the last dose received in Part B. 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 5. Part C will be of 12 months' duration from the date the last patient enters this part of the study.

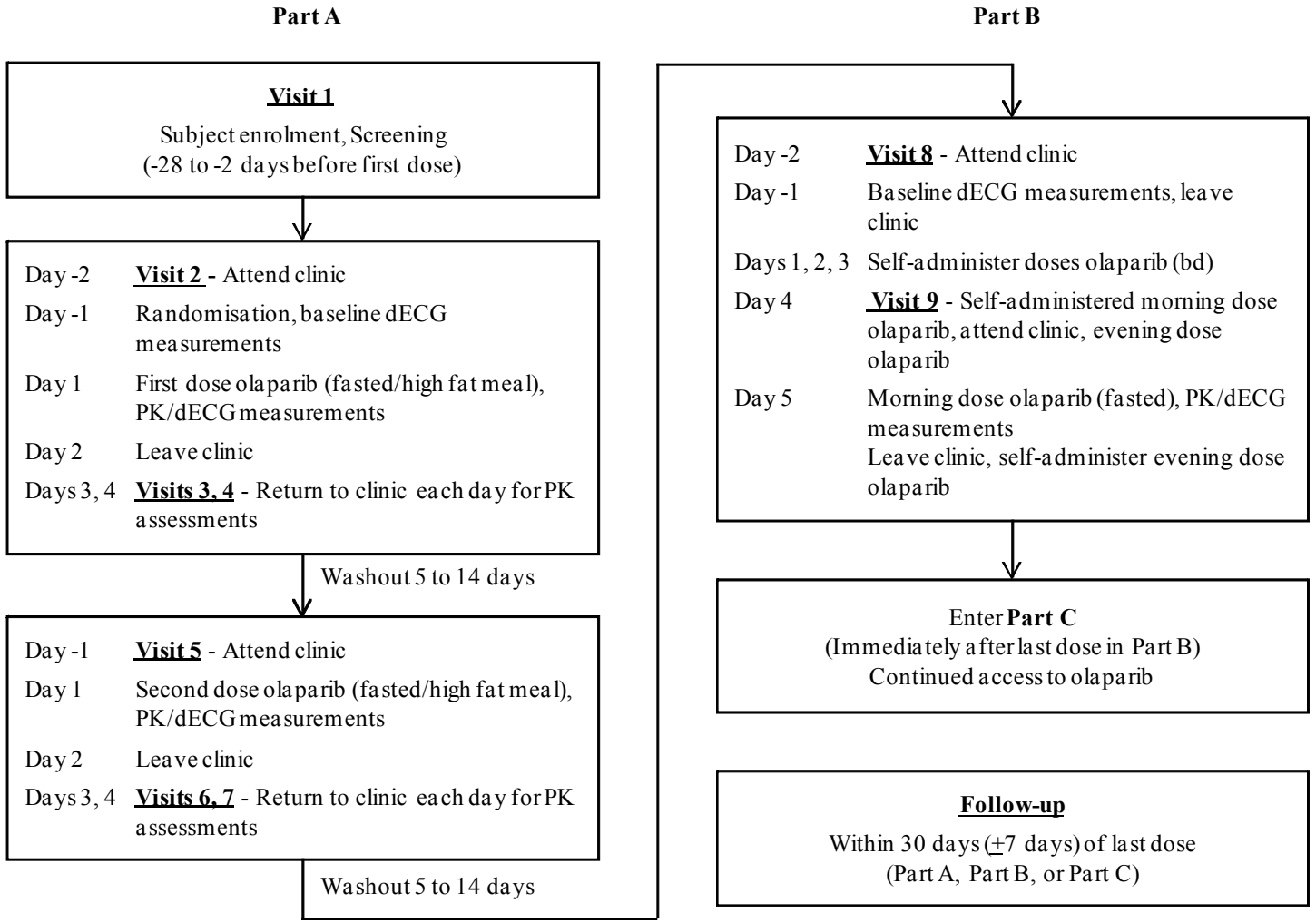
During and after Part C, patients may continue to take olaparib tablets, if they and the investigator deem it appropriate, until such time as their disease progresses, the investigator believes they are no longer deriving clinical benefit, or they stop taking olaparib tablets for any other reason. After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

Patients will return to the clinic for follow-up assessments either 30 days (±7 days) after their last dose (regardless of whether the last dose is in Part A, Part B, Part C, or the continued access phase after Part C). If a patient discontinues olaparib tablets during Part C, they will also attend a study treatment discontinuation visit.

Patients aged ≥18 years with advanced solid tumours who are refractory to standard therapy and are able to eat a high-fat meal will be recruited.

A flow chart illustrating Parts A, B, and C of the study is provided in Figure 1.

Figure 1 Study flow chart



bd twice daily; dECG digital electrocardiogram; PK pharmacokinetics

Table 3 Study plan – Part A

Assessments	**Screening**	**Treatment Period (TP) 1 and 2[a]**						**Washout[b]**	**Follow-up[c]**
Visits	**1**	**<--------2 (TP 1)-------> <--------5 (TP 2)------->**				**3 6**	**4 7**		
Day[d]	**-28 to -2 days before TP 1 dose**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5-14 days**	**30 (±7) days after last dose**
Resident in clinic		<----------[e]							
Outpatient visits	X					X	X		X
Informed consent	X								
Demography	X								
Medical/surgical history	X								
Inclusion/exclusion criteria	X								
Germline BRCA status[f]	X								
ECOG performance status	X								
Height	X								
Body weight	X								
Physical exam	X	X	X[e]						X
Vital signs (BP, pulse)	X	X	X						X
Oral temperature	X	X	X						
Resting standard 12-lead ECG	X	X	X[e]						X
Haematology/biochemistry/ coagulation[g]	X	X	X[e]						X
Urinalysis[h]	X	X	X[e]						X
Serum/urine pregnancy test[i]	X			X					
Randomisation[a]			X						
Olaparib administration[j]				X					

Table 3 Study plan – Part A

Assessments	Screening	Treatment Period (TP) 1 and 2[a]						Washout[b]	Follow-up[c]
Visits	**1**	**<--------2 (TP 1)-------> <--------5 (TP 2)------->**				**3 6**	**4 7**		
Day[d]	**-28 to -2 days before TP 1 dose**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5-14 days**	**30 (±7) days after last dose**
Resident in clinic		<----------[e]							
Outpatient visits	X					X	X		X
Olaparib PK blood sampling[k]				X	X	X	X		
Serial dECG measurements[l]			X[e]	X	X				
Adverse events[m]	X	X	X	X	X	X	X	X	X
Prior and concomitant meds	X	X	X	X	X	X	X	X	X

[a] Patients will be randomised to receive 2 single doses of olaparib under fasted or fed conditions (after a high-fat meal) during 2 treatment periods (TP 1 and TP 2). Randomisation of each patient to the order of these treatments will occur on the evening of Day -1 of TP 1.

[b] There will be a minimum of a 5-day and a maximum of a 14-day washout period between the 2 olaparib doses in Part A, and between the last olaparib dose in Part A and Day -1 of Part B.

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

[d] There is no Day 0. Day 1 is the day of dosing; Day -1 is the day before dosing.

[e] Patients will check into the clinic on the evening of Day -2 for TP 1 and on the evening of Day -1 for TP 2. During TP 1, patients will undergo baseline dECG assessments on Day -1 over a 24-hour period. If patients are unable to check into the clinic on Day -2 and complete the Day -1 dECG assessments immediately prior to dosing (ie, Day 1), the baseline confinement and measurements can be completed within 3 days of dosing. During TP 1, physical exam, resting standard 12-lead ECG, haematology/biochemistry, and urinalysis will not be performed on Day -1.

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

[g] Coagulation (aPTT and INR) will be performed at baseline and if clinically indicated unless the patient is receiving warfarin.

[h] Protein, blood, glucose and bilirubin.

[i] 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 treatment at Visit 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.

[j] Patients will receive olaparib 2 x 150 mg tablets orally on Day 1 of each treatment period. In the fasted treatment period, patients should be fasted from at least 10 hours prior until 4 hours post-dose (patients may have a light snack if they have signs or symptoms of hypoglycaemia after they have received olaparib in the fasted state). In the fed treatment period, patients should be fasted from at least 10 hours prior until 4 hours post-dose, except for the consumption of a high-fat meal just prior to the olaparib dose. Patients should eat the meal within 30 minutes (if the patient is unable to eat the meal in

30 minutes, they will still be considered evaluable as long as they have consumed at least 75% within 45 minutes). The olaparib should be administered 30 minutes after the start of the meal (or maximum 45 minutes after the start, if the meal is not completed). For full details, see Section 5.5.2.1.

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

[l] dECGs will be recorded on Day 1 of each treatment period at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after olaparib dosing. Additionally, on Day -1 of TP 1 (baseline), dECGs will be recorded at time points that are clock-time matched to each of the planned/scheduled measurements on Day 1 of TP 1 (see Table 6). On Day -1 of TP 1, patients should be fasted from at least 10 hours before the first dECG measurement on Day -1 until the 4-hour post-dose dECG measurement on Day -1 is completed. The dECGs performed on Day 1 in each treatment period will be clock-time matched to the actual times that the Day -1 dECGs are performed in TP 1.

[m] 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.

AE adverse event; BP blood pressure; BRCA breast cancer gene; eCRF electronic case report form; dECG digital electrocardiogram; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; IP investigational product; PK pharmacokinetics; SAE serious adverse event; TP 1 Treatment Period 1; TP 2 Treatment Period 2

Table 4 Study plan – Part B

Assessments	**Treatment Period**							**Follow-up**[a]
Visits	**<---8--->**					**<---9--->**		
Day[b]	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**[c]	**30 (±7) days after last dose**
Resident in clinic	<------->					<------->		
Outpatient visits								X
Inclusion/exclusion criteria	X							
ECOG performance status	X							
Physical examination								X
Vital signs (BP, pulse)		X					X	X
Oral temperature		X						
Resting standard 12-lead ECG	X							X
Haematology/biochemistry		X					X	X
Urinalysis[d]		X						X
Serum/urine pregnancy test[e]		X						
Olaparib administration[f]			X	X	X	X	X	
Fasting[g]		X	X	X	X	X	X	
Olaparib PK blood sampling[h]							X	
Serial dECG measurements[i]		X					X	
Concomitant medications	X	X	X	X	X	X	X	X
Adverse events[j]	X	X	X	X	X	X	X	X

[a] For patients who withdraw from the study prematurely or do not participate in Part C.
[b] There is no Day 0. Day 1 is the day of dosing; Day -1 is the day before dosing.
[c] For patients who continue into Part C of the study, this visit serves as the first visit in Part C.
[d] Protein, blood, glucose and bilirubin. Urinalysis should be repeated only if clinically indicated.
[e] A pregnancy test will be conducted at baseline, but should be repeated in the event of a suspected pregnancy during the study.

[f] Patients will receive olaparib 2 x 150 mg tablets orally twice daily. Doses from Day 1 until the morning of Day 4 will be self-administered by the patients under fasted conditions (no food from 1 hour prior to 2 hours after dosing). Doses on the evening of Day 4 and the morning of Day 5 will be administered at the clinic by clinic personnel. The Day 5 evening dose will be self-administered by the patients.

[g] On the morning of Day 5, patients should be fasted from at least 10 hours prior until 4 hours after the morning dose. For all other olaparib doses, patients should be fasted from at least 1 hour prior until 2 hours after dosing. On the morning of Day -1, patients should be fasted over the same time period as the morning of Day 5.

[h] Olaparib PK samples will be collected on Day 5 at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the morning dose (see Table 7).

[i] dECGs will be recorded on Day 5 at pre-dose, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the morning dose. Additionally, on Day -1 (baseline), dECGs will be recorded at time points that are clock-time matched to the planned/scheduled measurements on Day 5 (see Table 7). The dECGs performed on Day 5 will be clock-time matched to the actual times that the Day -1 dECGs are performed . If patients are unable to check into the clinic on Day -2 and complete the Day -1 dECG assessments immediately prior to start of dosing (ie, Day 1), the baseline confinement and measurements can be completed within 3 days of dosing, as long as there has been at least a 5-day washout between the last olaparib dose and the first baseline dECG measurement.

[j] 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.

AE adverse event; BP blood pressure; dECG digital electrocardiogram; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; IP investigational product; PK pharmacokinetics; SAE serious adverse event

Table 5 Study plan - Part C (continued access to olaparib tablets)

Visit Number	**Additional to Visit 9, Day 5, Part B[a]**	**10**	**11**	**12**	**13**	**Subsequent on-treatment visits every 4 weeks[b]** **Visit 14 onwards**	**Study treatment discontinued**	**Follow-up 30 (±7) days after last dose of study medication**
Day		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	0-7d	±7d
Physical examination[c]		X	X	X	X	X	X	X
Vital signs (BP, pulse, temperature)		X	X	X	X	X	X	X
Resting standard 12-lead ECG						X		X
Haematology/clinical chemistry		X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X
Olaparib dispensed/returned[d]	X[e]				X[d]	X[d]	X	

[a] The last visit in Part B (Visit 9, Day 5) will serve as the first visit in Part C.
[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 C.
[c] After baseline, it is not necessary to record any physical examination details on the eCRF; any clinically significant changes should be recorded as AEs.
[d] 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.
[e] The return and dispensing of olaparib should be on the evening of Visit 9 (Day 5) in Part B.

Note: Urinalysis will be conducted only if clinically indicated.
Note: A pregnancy test will be conducted only in the event of a suspected pregnancy during the study.
AE adverse event; BP blood pressure; eCRF electronic case report form; ECG electrocardiogram

Table 6 Timing of PK samples and dECG measurements – Part A

Treatment Period, Day	Time (hours)	IP	dECG (12-lead)	PK blood
TP 1 only, Day -1	Pre-dose		+[b]	
	0.5		+[b]	
	1		+[b]	
	1.5		+[b]	
	2		+[b]	
	3		+[b]	
	4[a]		+[b]	
	6		+[b]	
	8		+[b]	
	12		+[b]	
TP 1 and TP 2, Day 1	Pre-dose		+[c]	+
	Dose	+[d]		
	0.25			+
	0.5		+[c]	+
	1		+[c]	+
	1.5		+[c]	+
	2		+[c]	+
	3		+[c]	+
	4[a]		+[c]	+
	6		+[c]	+

Table 6 Timing of PK samples and dECG measurements – Part A

Treatment Period, Day	Time (hours)	IP	dECG (12-lead)	PK blood
	8		+[c]	+
	12		+[c]	+
TP 1 and TP 2, Day 2	24		+[c]	+
TP 1 and TP 2, Day 3	48			+
TP 1 and TP 2, Day 4	72			+

[a] For Day -1 of TP 1 and for Day 1 of the fasted treatment period, patients will be fasted from the previous night until completion of all measurements at this 4-hour time point; patients may have a light snack (described in Appendix G) between dosing and the 4 hour time point if they have signs or symptoms of hypoglycaemia after dosing. For Day 1 of the fed treatment period, patients will follow this same fasting schedule, except for their consumption of a high-fat meal prior to dosing.

[b] dECGs on Day -1 of TP 1 (baseline) are to be recorded at time points that are clock-time matched to each of the planned/scheduled measurements on Day 1 of TP 1. For example, if measurements on Day 1 of TP 1 are scheduled at 07:00 (pre-dose measurement), 08:30 (0.5 hour), 09:00 (1 hour), 09:30 (1.5 hour), etc, then measurements on Day -1 will be done at the same clock times (ie, 07:00, 08:30, 09:00, etc).

[c] During TP 1, this dECG measurement will function as both the 24-hour measurement for Day -1 and the pre-dose measurement for Day 1. If the baseline dECG measurements are recorded on a day prior to Day -1, then separate baseline 24-hour and Day 1 pre-dose measurements will be required. The dECGs performed on Day 1 in each treatment period will be clock-time matched to the actual times that the Day -1 dECGs are performed in TP 1.

[d] When receiving fed treatment, patients should eat the meal in 30 minutes or less, and olaparib should be administered 30 minutes after the start of the meal. Pre-dose measurements are to be collected before the start of the meal.

dECG digital electrocardiogram; IP investigational product; PK pharmacokinetics; TP 1 Treatment Period 1; TP 2 Treatment Period 2

Table 7 Timing of PK samples and dECG measurements – Part B (Days -1 and 5)

Day	Time (hrs)	IP	dECG (12-lead)	PK blood
Day -1	Pre-dose		+[b]	
	1		+[b]	
	1.5		+[b]	
	2		+[b]	
	3		+[b]	
	4[a]		+[b]	
	6		+[b]	
	8		+[b]	
	12		+[b]	
Day 5[c]	Pre-dose		+	+
	Dose	+		
	0.5			+
	1		+	+
	1.5		+	+
	2		+	+
	3		+	+
	4[a]		+	+
	6		+	+
	8		+	+
	12[e]	+	+	+

[a] Patients will be fasted from the previous night until completion of all measurements at this 4-hour time point. Patients may have a light snack (described in Appendix G) between dosing and the 4 hour time point if they have signs or symptoms of hypoglycaemia after dosing.

[b] dECGs on Day -1 will be recorded at time points that are clock-time matched to planned/scheduled measurements on Day 5. For example, if measurements on Day 5 are scheduled at 07:00 (pre-dose measurement), 08:30 (0.5 hour), 09:00 (1 hour), 09:30 (1.5 hour), etc, then measurements on Day -1 will be done at the same clock times (ie, 07:00, 08:30, 09:00, 09:30, etc).

[c] Relative to the Day 5 morning dose.

[d] The dECGs performed on Day 5 will be clock-matched to the actual times that the Day -1 dECGs are performed .

[e] Administration of IP at 12 hours is not to occur until AFTER the PK and dECG samples have been collected.

dECG digital electrocardiogram; IP investigational product; PK pharmacokinetics

3.2 Rationale for study design, doses and control groups

The food-effect part of this study has been designed as a 2-treatment period crossover study to allow the investigation of the effect of food within each patient and in a randomised manner. A crossover design is the recommended design for food effect studies to reduce inter-patient variability.

Due to existing pre-clinical data it is not possible to use healthy volunteers for this study. It is therefore relevant to use 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.

4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, the patient screening log of patients 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 patients should fulfil the following criteria:

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

2. Patients aged ≥18 years

3. Able to eat a high-fat meal within a 30-minute period, as provided by the study site

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

5. Normal organ and bone marrow function measured within 28 days prior to administration of investigational product (IP) as defined below:

   - Haemoglobin ≥10.0 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 ≥100 x 10^9/L

- Total bilirubin ≤1.5 x institutional upper limit of normal (ULN) except in the case of Gilbert's disease

- Aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤2.5 x institutional ULN unless liver metastases are present in which case it must be ≤5x ULN

- Serum creatinine ≤1.5 x institutional ULN

- Serum potassium >4 mmol/L and within the institutional normal range

- Other serum electrolytes (sodium, magnesium, and calcium) within the institutional normal range

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

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

8. Patients must have a life expectancy of ≥16 weeks.

9. Evidence of non-childbearing status for women of childbearing potential, or post-menopausal 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 post-menopausal 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)

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

11. Patients must be on a stable concomitant medication regimen, defined as no changes in medication or in dose within 2 weeks prior to start of olaparib dosing, except for bisphosphonates, denosumab, and corticosteroids, which should be stable for at least 4 weeks prior to start of olaparib dosing.

4.2 Exclusion criteria

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

2. Previous enrolment in the present study

3. Participation in another clinical study with an IP during the last 14 days (or a longer period depending on the defined characteristics of the agents used)

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

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

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

7. Patients who have received or are receiving inhibitors or inducers of CYP3A4 (see Section 5.6.1 for guidelines and washout periods)

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

9. 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.

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

11. Patients unable to fast for up to 14 hours

12. 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 computed tomography (HRCT) scan, or any psychiatric disorder that prohibits obtaining informed consent.

13. Patients with a history of poorly controlled hypertension with resting blood pressure (BP) >150/100 mm Hg in the presence or absence of a stable regimen of hypertensive therapy. Measurements will be made after the patient has been resting supine for a minimum of 5 minutes. Two or more readings should be taken at 2-minute intervals and averaged. If the first 2 diastolic readings differ by more than 5 mm Hg, an additional reading should be obtained and averaged.

14. Patients with a history of heart failure or left ventricular dysfunction, and patients who require calcium channel blockers

15. Patients with type I or type II diabetes

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

17. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the olaparib, and patients who have had previous gastrointestinal resection

18. Breastfeeding women

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

20. Patients with known active hepatic disease (ie, hepatitis B or C)

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

22. Mean QTc with Fridericia's correction (QTcF) >470 ms in screening ECG or history of familial long QT syndrome:

    - a marked baseline prolongation of QT/QTc interval (eg, repeated demonstration of a QTc interval >470 ms)

    - a history of additional risk factors for Torsade de pointes (eg, heart failure, hypokalaemia, family history of long QT syndrome)

23. The use of concomitant medications that prolong the QT/QTc interval

24. Patients who receive a seasonal flu vaccine (including H1N1, H1N5) must defer enrolment for 28 days post vaccination.

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

For 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 Parts A, B, and C of the study, unless otherwise specified:

Contraception

Patients of childbearing potential and their partners, who are sexually active, must agree to the use of 2 highly effective forms of contraception throughout their participation in the study and for 3 months after last dose of IP. Reliable methods of contraception should be used consistently and correctly; acceptable methods include barrier methods, implants, injectables, combined oral contraceptive methods, some intrauterine devices (IUDs), sexual abstinence or vasectomised partner. See Appendix F for details of acceptable birth control methods to be used within the study.

Other concomitant treatment

For restrictions regarding concomitant medications, please see Section 5.6.

Other restrictions

1. Part A, fasted treatment: Patients will be fasted from at least 10 hours before olaparib dosing until 4 hours post-dose on Day 1. However, patients may have a light snack (see Appendix G) if they have signs or symptoms of hypoglycaemia after they have received olaparib tablets in the fasted state. Water can be allowed as desired except for 1 hour before and after olaparib administration. The time and exact nature of any additional food consumed must be recorded in the electronic case report form (eCRF).

   Part A, fed treatment: Patients will be fasted for at least 10 hours after which they will be given a high-fat meal. Patients should eat the meal within 30 minutes (in the event the patient is unable to eat the meal in 30 minutes, they will still be considered evaluable as long as they have consumed at least 75% of it within 45 minutes). The olaparib tablets should be administered 30 minutes after the start of the meal (or a maximum of 45 minutes after the start of the meal, if the meal is not completed), after which patients will fast until 4 hours post-dose. Water can be allowed as desired except for 1 hour before and after olaparib administration.

   Also on Day -1, patients will be fasted over the same time period as Day 1 of Treatment Period 1.

Part B: Patients will be fasted from at least 10 hours before the Day 5 morning dose of olaparib tablets until 4 hours post-dose and over the same time period on Day -1. However, patients may have a light snack (see Appendix G) if they have signs or symptoms of hypoglycaemia after they have received olaparib tablets in the fasted state. For all doses of olaparib tablets on Days 1 to 4 and the Day 5 evening dose of olaparib tablets, patients should take the dose at least 1 hour after food, and the patient should then refrain from eating for a further 2 hours. Tablets should be swallowed whole and not chewed, crushed, or divided.

Water will be restricted from 1 hour pre-dose until 1 hour post-dose for all treatments in Part A and for the Day 5 morning dose in Part B, except for the water administered with olaparib tablets. On Day -1 of Part A and Day -1 of Part B, timings of water restrictions will clock-match the corresponding olaparib dosing days.

2. On days when dECG measurements are being taken, patients should be restricted to a low level of physical activity and should refrain from any activities likely to stimulate or excite them (eg, video games, stimulating movies or television shows, etc). Additionally, they should refrain from using hand-held electronic or electrical devices (eg, cell phones, hair dryers, etc) as these have a potential to interfere with ECG signals.

5.2 Patient enrolment and randomisation and initiation of investigational product

The PI will:

1. Determine patient eligibility. See Sections 4.1 and 4.2

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

3. Assign each potential patient a unique enrolment number code (E-code) beginning with ‘E#’ after written informed consent has been obtained. The E-code (EXXXXYYY) will consist of a 4-digit centre number (XXXX) and a 3-digit serial number (YYY, starting with 001) issued by the study centre in order of informed consent taken.

4. Assign eligible patients a unique randomisation number (see Section 5.2.1).

5.2.1 Procedures for randomisation

Patient eligibility will be established before treatment randomisation. Patients will be randomised strictly sequentially, as patients are confirmed as eligible to receive treatment, and the patients will not be allowed to re-enter the study.

The actual sequence given to individual patients will be determined by a randomisation scheme prepared by the Biostatistics Group, AstraZeneca. The randomisation schedule will be allocated in blocks and will be produced by computer software that incorporates a standard procedure for generating random numbers.

Investigational sites will be provided with sealed envelopes with randomisation numbers pre-printed on the cover. The sequence allocated to a specific randomisation number will be contained within the corresponding sealed envelope. A randomisation number which will identify the sequence assigned to an individual patient will be allocated strictly sequentially upon confirmation of eligibility to receive study treatment. Once allocated, the appropriate randomisation code envelope should be opened to identify the sequence that patient will receive. The opened randomisation code envelopes will be stored in the investigator site file.

Patients will be randomised to 1 of the following 2 treatment sequences (24 patients per sequence) in Part A:

Table 8 Treatment sequences, Part A

Sequence	Treatment Period 1	Treatment Period 2
1	Fasted	High-fat meal
2	High-fat meal	Fasted

5.3 Procedures for handling patients incorrectly enrolled or randomised

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

Where patients that do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation (in either Part A or Part 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)

AstraZeneca Pharmaceutical Supply Chain will supply olaparib to the investigator as plain, green film-coated biconvex tablets as follows:

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

[a] Descriptive information for olaparib can be found in the IB.

For all sites, olaparib tablets will be packed in high density polyethylene (HDPE) bottles with child resistant closures. In Part A and Part B of the study, patients will be dispensed the exact amount of olaparib tablets for each dosing visit. In Part C 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 2 single doses of 300 mg olaparib comprised of 2 x 150 mg tablets. Dosing will occur at approximately 08:00. The IP 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 IP. 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 tablets, all PK sampling may be omitted for that treatment period but the safety assessments should continue as per the study schedule. The patient may proceed to further treatment periods in Part A, if applicable, and then onto Parts B and C.

Fasted Treatment: Patients should be administered olaparib tablets following an overnight fast of at least 10 hours. No food should be allowed for at least 4 hours post-dose. However, patients may have a light snack (see Appendix G) if they have signs or symptoms of hypoglycaemia after they have received olaparib tablets in the fasted state. The time and exact nature of any additional food consumed must be recorded in the eCRF. Water can be allowed as desired except for 1 hour before and after olaparib administration.

Fed Treatment (high-fat meal): Following an overnight fast of at least 10 hours, patients should consume the recommended meal prior to administration of olaparib tablets. Patients should eat the meal within 30 minutes (in the event the patient is unable to eat the meal in 30 minutes, they will still be considered evaluable as long as they have consumed at least 75% of it within 45 minutes. If a patient does not eat at least 75% of the meal within 45 minutes,

then they will be non-evaluable for that treatment period and will not be dosed or sampled for PK in that treatment period. It may be possible for such patients to defer Day 1 by another day, if this is still within the defined washout window, but this must be discussed and agreed with the Investigator on a case-by-case basis). The olaparib tablets should be administered 30 minutes after the start of the meal (or a maximum of 45 minutes after the start of the meal, if the meal is not completed in 30 minutes). No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for 1 hour before and after olaparib administration.

In accordance with FDA guidance (Food and Drug Administration 2002), the high-fat meal should have a total calorie content of approximately 800 to 1000 kcal, with approximately 50% of the calorie content made up from fat. The meal should therefore derive approximately 150, 250 and 500 to 600 kcal from protein, carbohydrate and fat respectively. For an example of a high-fat meal, see Appendix G. The composition of the meal supplied to each patient should be documented in the raw data together with the amount eaten and time period over which it was eaten. The same meal should be provided to all patients dosed at each investigational site.

5.5.2.2 Part B

For Part B of the study, each patient will take a total of 10 doses of 300 mg olaparib, comprising 2 x 150 mg tablets given orally bd for 5 days. The doses from Day 1 up to the morning of Day 4, and the Day 5 evening dose of olaparib tablets, will be self-administered by the patient. Patients should aim to take their doses at similar times each day, approximately 12 hours apart (between approximately 07:00 to 09:00 and 19:00 to 21:00). Patients will be instructed to take their doses of olaparib tablets at least 1 hour after food, and the patient should then refrain from eating for a further 2 hours. The evening dose on Day 4 and the morning dose on Day 5 will be administered by the investigator or his/her delegate at the clinic. The morning dose on Day 5 MUST be taken fasted, ie, for at least 10 hours prior to until 4 hours post dose. The olaparib tablets should be swallowed whole with approximately 240 mL glass of water, and not chewed, crushed, dissolved or divided. Patients may have a light snack (see Appendix G) if they have signs or symptoms of hypoglycaemia after they have received olaparib tablets in the fasted state. The time and exact nature of any additional food consumed must be recorded in the eCRF.

5.5.2.3 Part C

Patients who are eligible to continue in Part C will receive 300 mg bd oral olaparib (comprising 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 study treatment can be taken with a light meal/snack. The olaparib tablets should be swallowed whole with a glass of water, and not chewed, crushed, dissolved or divided.

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.

The label will include the following information: the study number and a statement that the drug is for clinical trial use only and should be kept out of reach of children.

5.5.5 Storage

All IP should 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 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 eCRF.

Olaparib is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib.

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

- ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin, and nelfinavir

For patients taking any of the above, the required washout period prior to starting olaparib is 1 week.

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

- phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil, and St. John’s Wort

For patients taking any of the above, the required washout periods prior to starting olaparib are:

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

If the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare during Part C, the investigator must contact the AstraZeneca Physician or 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.

5.6.2 Other concomitant medications

Other medications, with the exceptions noted in Section 5.6.5, which are considered necessary for the patient's safety and well being, 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 appropriate sections of the eCRF.

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 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.

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 C of the study (see Section 5.10).

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

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 eCRF.

5.6.3 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.

5.6.4 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).

5.6.5 Medications that may NOT be administered

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

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.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

5.7 Treatment compliance

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

When patients are in 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.

Adequate compliance during the outpatient period will be defined as follows in Part B: The patient should not have missed more than 1 dose, and the missed dose should not have occurred on Days 3 or 4. Patients should aim to take their doses on outpatient days at similar times each day, approximately 12 hours apart, between 07:00 to 09:00 and between 19:00 to 21:00 (ie, within ±1 hour of planned dose time on Day 5). They should be instructed that the dose is to be taken with a glass of water at least 1 hour after any food, and that they should not have any food for at least 2 hours after taking the dose.

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. Patients will need to complete diaries, which will record the date/time of each dose (all dosing days), and for Day 4, the times of meal/snacks taken prior to and after the dose.

For Part C, patients 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. The study treatment can be taken with a light meal/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 eCRF. 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 tablets at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded on the eCRF. Patients must return all bottles and any remaining tablets when they discontinue IP.

5.7.1 Accountability

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

- Deliveries of such products from AstraZeneca 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 to and returned from the patient.

Study site personnel or the AstraZeneca monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery and destruction should be signed.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the 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 eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return should 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 C for as long as patients continue to receive IP.

5.8 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations (applies to Parts A, B, and C):

- 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 C).

5.8.1 Procedures for discontinuation of a patient from investigational product

If a patient discontinues IP during Part C, then they will attend a study treatment discontinuation visit and follow the procedures described in Table 5.

As described in Section 3.1, a patient may remain on study treatment after Part C 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) and the presence of any AEs. If possible, they will be seen and assessed by an investigator(s). AEs will be followed up (see Sections 6.3.3 and 6.3.4) 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 eCRF 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. 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 6.3.3 and 6.3.4). 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 6.3.4) 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 study, see Section 5.9.

5.9 Withdrawal from study

Patients are at any time free to withdraw from 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 6.3.3 and 6.3.4) and diaries 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 a guidance for investigators who treat patients with olaparib tablets in Part C.

Where toxicity reoccurs following re-challenge with olaparib tablets, 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-week (14-day) 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 tablets, but with a dose reduction according to Table 9. If the event recurs with the same severity, treatment should be interrupted again and, on resolution, a further dose reduction made. A maximum of 2 dose reductions may be made. If, on the resumption of treatment after a 2nd dose reduction, the event continues to occur, the patient should permanently discontinue olaparib.

For surgery, olaparib tablets should be stopped at least 3 days prior to planned surgery. After surgery, olaparib tablets can be restarted when the wound has healed. No stoppage of olaparib tablets 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 should not be adjusted under any other circumstances without consulting the AstraZeneca Physician or their representative. Once the dose of olaparib has been reduced, it should not be re-escalated.

Olaparib tablets should be discontinued for a minimum of 7 days before a patient undergoes therapeutic radiation treatment. This is not required where palliative doses are used.

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

Table 9 Dose reductions for olaparib in Part C 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 1x100 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 $<1x10^9$/L)
- ≥2 week interruption/delay in study treatment due to CTCAE Grade 3 or higher thrombocytopenia (platelets $<50x10^9$/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 $>1.5x10^9$/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. 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 eCRFs as specified in the study protocol and in accordance with the instructions provided.

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

6.2 Data collection at enrolment and follow-up

The study assessments and the timing of these assessments are detailed in Table 3, Table 4, and Table 5.

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. dECG
2. Vital signs (if applicable)
3. PK blood sample (at scheduled time)
4. Any other assessments

For pre-dose assessments, dECG, vital signs, and PK samples should be collected within 60 minutes prior to dosing (for the fed treatment, they should occur prior to the meal).

6.2.1 Enrolment procedures

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
- 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, oral temperature), ECG, body weight, and height
- Haematology, clinical chemistry, 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.

6.2.2 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
- 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 (Part A and Part B follow-up only)
- Recording of any AEs or concomitant medications

6.2.3 Post study

After Part A and Part B are completed, for patients who do not enter Part C, no further clinical data (other than SAEs) will be collected for this part of the study and these patients will then resume the regular follow-up schedule as suggested by their physician.

After Part C is completed (12 months from the date the last patient enters this part of the study), patients may continue to take olaparib tablets (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 (Section 6.3.3).

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

6.3 Safety

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

6.3.1 Definition of adverse events

An 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.

6.3.2 Definitions of serious adverse event

An 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.

6.3.3 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 in Part A and Part B up to and including the 30-day follow-up period. In Part C, AEs will be collected until 12 months after the last patient entered Part C, and including the 30 day follow-up period for any patients who discontinue. After the end of Part C, 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 (see Section 5.8.1). 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 AstraZeneca Patient Safety or its representative within the usual timeframe (Section 6.3.4).

Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- 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 study (yes or no)
- Outcome

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- 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 v4.03 will be utilised for all events with an assigned CTCAE grading (CTCAE v4.03 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 6.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not 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 IP?'

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

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 eCRF. 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 Hb 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. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

New cancers

The development of a new primary cancer (including skin cancers) should be regarded as an AE and will generally meet at least 1 of the serious criteria (see Section 6.3.2). New primary cancers are those that are not the primary reason for the administration of the 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 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 eCRF but should not be reported as an SAE.

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

6.3.4 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 eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel must 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 1 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 must 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 AstraZeneca representative will advise the investigator/study site personnel how to proceed.

6.3.5 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 plan (Table 3, Table 4, and Table 5).

The following laboratory variables will be measured:

- Full haematology assessments for safety (Hb, red blood cells [RBC], platelets, mean corpuscular volume [MCV], mean corpuscular haemoglobin concentration [MCHC], mean corpuscular haemoglobin [MCH], WBC, differential white cell count and ANC should be performed at each visit and when clinically indicated. Coagulation (aPTT and INR) will be performed at baseline and if clinically indicated unless the patient is receiving warfarin.

- Chemistry 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.

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 performed on Day -1, but should be repeated in the event of a suspected pregnancy during the study. In Part C, a pregnancy test will be conducted 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 eCRF.

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.

6.3.6 Physical examination

Physical examinations will be conducted at the times specified in the study plan (Table 3, Table 4, and Table 5). Physical examinations conducted during Part C will not be captured on the eCRF. If new or aggravated physical findings imply deterioration compared with baseline, the finding should be reported as an AE.

Performance status will be assessed using the ECOG scale (see Appendix H) (see Table 3 and Table 4).

6.3.7 ECG

6.3.7.1 Digital ECG measurements

A central ECG laboratory will perform the ECG analysis in the study, using a flash card-based digital 12-lead ECG Holter system to collect 12-lead ECG data.

At protocol-indicated time points, 12-lead continuous dECGs will be recorded and sent to the central ECG laboratory, according to the central ECG laboratory's standard procedures for settings, recording, and transmission of dECGs.

Date and time settings must be checked at the start of each study day and aligned with an official timekeeper for all machines used in the study.

Skin preparation must be thorough and electrode positions must be according to standard 12-lead ECG placement appropriate for a Holter device. Electrode positions will be marked with an indelible pen at the start of the study days to ensure exact reposition. Permanent electrodes will be applied at least 30 minutes before the first study recording and left in place for the duration of each relevant study day. Patients should rest in supine position for at least 10 minutes before start of every recording. The patient should be in the same supine body position (maximum 30 degrees flexion in hip and feet not in contact with the footboard) at each recording time point during the study.

In this study, Lead II will be analysed and reported as primary. Lead V5 will be analysed as a backup where analysis in Lead II is not deemed possible.

ECG snapshots will be extracted in triplicates from the Holter flashcard at each of the specified time points by the Holter team at the central ECG laboratory. Each ECG replicate will be analysed by readers who will be blinded to patient identifiers and treatment. ECGs will be analysed for PR, QRS, RR and QT intervals. All ECGs from a single patient will be read together by the same reader and in a random sequence. Efforts will be made so that a single reader will review all ECGs of a patient on 1 day. All ECGs of a patient will be read in the same lead as allowed by the data. The lead used with alternatives will be prespecified in the ECG Operations Plan.

6.3.7.2 Resting 12-lead ECG

A 12-lead safety ECG (paper ECG printout of 10 seconds for investigator review) will be taken at the times specified in Table 3, Table 4, and Table 6.

When dECG and safety ECG recordings occur at the same time, the paper ECG should be printed at the end of the dECG recording.

The ECGs may be taken at any other time the investigator deems necessary for safety during the dosing period. The patients will rest at least 10 minutes before the start of each recording and they must be in the same supine (maximum 30 degrees flexion in the hip and feet not in contact with the footboard) body position at each recording time point during all visits.

The investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant. The paper copy of each ECG reading will be retained with the patients' completed source documents. Only overall evaluation (normal/abnormal) will be recorded in the appropriate database.

6.3.8 Vital signs

For timing of individual measurements of BP and pulse, refer to the study plan (see Table 3, Table 4, and Table 5). 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 rate 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.

6.4 Pharmacokinetics

For timing of individual samples, refer to the study schedule. Samples may also be used to investigate the presence of additional analytes if deemed appropriate.

6.4.1 Collection of samples

Venous blood samples (4 mL) for determination of olaparib in plasma will be taken at the time points detailed in the study plan (see Table 3 and Table 4). 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 eCRF.

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.

For blood volume see Section 7.1.

6.4.2 Determination of drug concentration

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

Additional analyses may be conducted on the PK samples to further investigate the presence and/or identity of drug metabolites and/or to investigate reproducibility of incurred samples. Any results from exploratory analyses to identify drug metabolites will not be reported in the CSR but will be reported separately elsewhere. Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report.

6.5 Pharmacodynamics

See Section 6.3.7.1 for procedures related to dECG collection and processing.

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 300 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, B, and C

Assessment		Sample volume (mL)	No. of samples				Total volume (mL)
			A[a]	B	C[b]	Follow-up	
Safety	Clinical chemistry	2.7 mL	3	2	18	1	64.8
	Haematology	2.7 mL	3	2	18	1	64.8
Pharmacokinetic	Olaparib	4 mL	28	10	0	0	152.0
Total volume (mL)			128.2	50.8	97.2	5.4	281.6

[a] Includes screening blood volumes.
[b] Number of samples in Part C is based on a patient being in the study for an estimated maximum of 15 months.

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 and/or pharmacodynamic 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.

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.

[redacted] 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 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 Ethics Committee and to the study site staff.

The opinion of the Ethics Committee 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 Ethics Committee 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 Ethics Committee 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, Ethics Committees 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(s) at each study 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 Ethics Committee.

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 Ethics Committee and if applicable, also the National Regulatory Authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to Ethics Committee 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 Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

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

8.6 Audits and inspections

Authorised representatives of AstraZeneca or its representative, a Regulatory Authority, or an Ethics Committee 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 [redacted] on behalf of AstraZeneca, and [redacted] will act as the AstraZeneca representative.

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 or its representative 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 eCRFs, 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 eCRFs 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, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study 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 to start dosing with olaparib tablets in Part B, whichever is later.

The end of Part B of this study is defined as either the 30-day follow-up date of the last patient to discontinue after Part B OR the date of the last patient to receive olaparib tablets on Day 5 of Part B, whichever is later.

The end of Part C of this study is defined as the date when all patients receiving olaparib tablets in Part C have been followed for a period of at least 12 months since the last patient entered Part C (defined as date of the last patient entered into Part C 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 tablets beyond the closure of the database if, in the opinion of the investigator, they are continuing to receive benefit from treatment with olaparib tablets. For patients who do continue to receive treatment beyond the defined end of the study, investigators will continue to report all SAEs to AstraZeneca Patient Safety until 30 days after IP is discontinued, in accordance with Section 6.3.4 (Reporting of serious adverse events). In addition, as stated in Section 6.3.3 (Recording of adverse events), any SAE or non-serious AE that is ongoing at the time defined as the end of the study, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. After the end of Part C (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 AstraZeneca Patient Safety database.

The study is expected to start in [redacted] Part A to be completed in [redacted] Part B to be completed in [redacted] and Part C to be completed in [redacted]

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.

10. DATA MANAGEMENT

Data management will be performed by [redacted]

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

AEs 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.

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 (DMP). 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 patients have completed Part A and Part B of the study (or at the request of AstraZeneca), an interim database lock will be provided. All Part A and Part B data for patients who have completed by the time of the interim database lock transfer will be cleaned and validated as defined in the DMP. On completion of Part C, a further database lock will occur and the Part C data will be reported. Separate CSRs will be provided, one for Parts A and B and one for Part C. See also Section 12.2.1.

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

11.1 Calculation or derivation of safety variable(s)

11.1.1 Other significant adverse events (OAE)

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

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

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

11.3 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 during each treatment 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
- Terminal rate constant (λ_z) estimated by log-linear least squares regression of the terminal part of the concentration-time curve
- 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 the addition of the last quantifiable concentration divided by the terminal rate constant: $AUC_{0-t}+C_{last}/\lambda_z$.
- Terminal half-life ($t_{1/2}$). Visual assessment will be used to identify the terminal linear phase of the concentration-time profile
- Apparent plasma clearance (CL/F)
- Apparent volume of distribution (V_z/F)

If sufficient data are available for estimation, the following multiple-dose PK parameters will be calculated for olaparib on Day 5 of Part B:

- 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
- Minimum plasma concentration (C_{min}) obtained directly from the observed concentration versus time data
- Time to minimum plasma concentration (t_{min}) obtained directly from the observed concentration versus time data
- Area under the plasma concentration-time curve over the dosing interval, τ ($AUC_{0-\tau}$), calculated by linear up/log down trapezoidal summation
- Average concentration over the dosing interval (C_{avg}) calculated as $AUC_{0-\tau}/\tau$
- Fluctuation index (FI), calculated as $[(C_{max}-C_{min})/C_{avg}]\times 100\%$
- Apparent plasma clearance (CL/F)

Additional PK parameters may be determined if deemed appropriate.

11.4 Calculation or derivation of pharmacodynamic variable(s)

The pharmacodynamic (PD) analyses of the dECG data will be performed by the designated contract research organization (CRO). The CRO's standard operating procedures (SOPs) and Work Instructions will be used as the default methodology if not otherwise specified.

The PD variables to be reported from the continuous dECG measurements are RR, PQ, QRS, and QT. Summaries and analysis will be conducted using data from the Lead II as the primary analysis lead, and using Lead V5 as a backup if Lead II is found to be unsuitable for analysis or evaluation.

The QT interval will be corrected for RR (the duration of a heart beat) to obtain corrected (QTc) variables.

The general formula for QTc that will be used is:

$QTc=QT/RR^b$

with the QT intervals expressed in milliseconds and the RR interval in seconds.

Different factors for b in the formula above will be used:

1. For QTcF b=1/3

2. For QTcB (Bazett-corrected) b=1/2

3. For individual QT correction (QTcI), individual values of b_i will be estimated for each patient from the study data.

For the estimates of the individual-specific correction factors, the estimate of individual slopes, b_i, a fixed effects linear model for patient i, part p, and time point t will be used:

$$\log(QT_{i,p,t})=a_{i,p}+b_i \log(RR_{i,p,t})$$

The corrected QT is then obtained by:

$$QTcI_{i,p,t}=QT_{i,p,t} / ((RR_{i,p,t})b_i)$$

The estimation will be based on the pooled data from the drug-free days: Day -1 in Part A, and Day -1 in Part B.

Additional methods of QT correction may also be applied.

The time points defined for the collection of PD data are specified in Table 6 and Table 7. To obtain a single PD value of QTcF, QTcB, RR, PR, and QRS at each specified time point, the mean of the triplicate values at that time point will be used.

Baseline for the PD data in Part A is defined as Day -1 of the fasted treatment in Part A, and baseline for the PD data in Part B is defined as Day -1 in Part B. For each patient, the change-from-baseline in a PD variable at each time point will be calculated as the difference between the mean of the replicate value at each post-dose time point and the mean of the time-matched replicate value at the corresponding baseline.

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.

Table 11 Definition of analysis sets

Set	Population
PK analysis set	All patients who receive an olaparib dose and provide evaluable PK profiles in at least 1 treatment period.
Evaluable for QT summaries	All patients who have at least 1 evaluable QT/QTc interval value at a scheduled post-dose/time matched to post-dose time point.
Evaluable for Safety	All patients who receive at least 1 dose of olaparib.

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

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

12.2 Methods of statistical analyses

The following text applies to demographic and safety analyses only; PK and PD (QT) are discussed separately.

Statistical analyses will be performed by [redacted] under the direction of the Biostatistics Group at AstraZeneca using SAS® v8.1 or higher and, where appropriate, additional validated software.

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

The number of patients screened and included in the 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 for Part C only. 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 and Part B

After the last patient has completed the treatment period in Part B, the database for Part A and Part B of the study will be locked and the data will be reported in a Part A and Part B CSR.

AstraZeneca anticipates receiving regulatory questions relating to QT effect of olaparib in relation to a marketing authorisation application submission planned for [redacted] In the event that Part A and Part B are not completed at the time of receipt of the questions, an analysis of the available Part A and Part B data may be performed to enable AstraZeneca to respond within the permitted time frame.

Part C

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

12.2.2 Pharmacokinetics

The sample bioanalysis will be performed by [redacted] The merging of PK concentration data with actual PK sampling times will be performed by [redacted] 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 [redacted]

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

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarised using descriptive statistics, including n, arithmetic mean, SD, coefficient of variation (%CV), median, minimum, and maximum values. Additionally, geometric means and geometric %CV (%GCV) will be reported for PK variables (concentrations and all PK parameters, except for t_{max}). The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The %GCV is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a log scale. Mean, SD,

%CV, geometric mean, and %GCV will not be calculated for t_{max}; t_{max} will be summarised by median and range.

For all data, descriptive statistics except for %CV and %GCV will follow the rounding convention of the individual data. Coefficients of variation (%CV and %GCV) will always be reported to 1 decimal place. Ratios and any corresponding confidence intervals (CIs) that are obtained during inferential statistical analysis shall be reported as a percent with at least 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_{min}, C_{max}, t_{min}, and t_{max}), all other derived PK parameters will be reported to 3 significant digits.

The PK data will be presented by treatment (fed/fasted) (Part A) or by part (Part B).

The goal of the statistical analysis in Part A is to estimate the effect of food on the PK of olaparib, given in the tablet formulation. Following log-transformation, C_{max} and AUC (or AUC_{0-t}, if AUC is not adequately estimable) of olaparib will be separately analysed by mixed-effect analysis of variance (ANOVA), fitting terms for treatment (food condition: fasted or high-fat meal), sequence and treatment period. Patient within sequence will be treated as a random effect in the model. Point estimates and adjusted 90% CIs for the difference in treatment (fasted or high-fat meal) will be constructed. The point estimate and adjusted 90% CIs will then be exponentially back transformed to provide point and CI estimates for the ratio of interest (ie, C_{max} or AUC of olaparib for the high-fat meal to C_{max} or AUC of olaparib in the fasted state). No food effect on the PK of olaparib will be concluded if the 2-sided 90% CIs for the ratios of AUC (or AUC_{0-t} as previously noted) and C_{max} are within the range of 0.80 to 1.25.

An analysis of t_{max} using the Wilcoxon Signed Rank Test, and the Lehman median estimator of difference (fed-fasted) and 90% CIs will also be presented.

12.2.3 Pharmacodynamics

The PD analysis (QT/QTc interval analysis) and the PD summaries, figures, and data listings will be the responsibility of the [redacted]

All data received will be presented in data listings. Pharmacodynamic summaries will be presented for patients in the PD analysis set, as defined in Section 12.1. Data from patients excluded from the PD 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.

The dECG intervals (absolute values and change from baseline) will be listed and summarised using descriptive statistics (n, mean, SD, %CV, median, minimum, and maximum). The QT/QTc outliers are defined as QT/QTc values following dosing that are greater than 450 ms or are increases from baseline greater than 30 ms. QT/QTc outliers will be highlighted in the data listings and summarised using the following categories: values that are greater than 450 ms to 480 ms or less; greater than 480 ms to 500 ms or less; and greater than 500 ms; or are increases from baseline of greater than 30 ms to 60 ms or less; and greater than 60 ms. The number and percentage of patients who meet the ECG outlier criteria at any assessment after start of IP will be tabulated by treatment (Part A) or study day (Part B).

Additionally, dECG data from this study will be pooled with data from another study(ies) and analysed by AstraZeneca using statistical methods and PK/PD modeling. The methodology for these analyses will be described separately from this protocol.

12.2.4 Safety

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

Appropriate summaries of AEs, laboratory data, vital signs, and ECGs will be produced. Adverse events will be summarised separately for Parts A, B, and C of the study. Laboratory data, vital signs, physical examination, oral temperature, and ECGs will be summarised by treatment period (fed/fasted) in Part A, by study day for Part B, and by study day (where appropriate) for Part C. 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 tablets as well as the number of AEs experienced will be summarised. AEs will be classified using the MedDRA system of nomenclature (preferred term and system organ class [SOC]). AEs reported before administration of olaparib tablets will be listed only and be referred to as "pre-treatment." Treatment emergence will be defined for each part of the study (A, B, and C) and, for Part A, for each treatment period (fed/fasted).

For each part (A, B, and C) or treatment period within part (for Part A), a treatment emergent AE (TEAE) will be defined as an AE with the start date (Part C) or start date and time (Parts A and B) on or after the first dose date (Part C) or first dose date and time (Parts A and B) for that part/treatment period and up to (not including) the date (Part C) or the date and time (Parts A and B) of the first dose of the next part/treatment period, or up to (and including) 30 days after the last dose date in case of last part/treatment period 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 and period within 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.

12.3 Determination of sample size

The primary objective of this study is to investigate the effect of food on the PK of olaparib following oral dosing of the tablet formulation in patients with advanced solid tumours. The study has been sized to provide an estimate of the difference between olaparib PK parameters in the fed and fasted states. Based on the estimate of within-patient SD for log AUC from Studies D0180C00002 and D0180C00003 of 0.26, and assuming a true food effect difference of 5%, 42 evaluable volunteers (21 per-sequence) will give 90% power of showing that the 90% CI for the food effect (ratio of geometric least-squares means of AUC or C_{max} in the fed state to the fasted state) lies entirely within the range of 0.8 to 1.25. A total of 48 patients will

be entered to ensure that 42 evaluable patients complete the study. nQuery v7.2 was used for the sample size calculations.

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 6.3.4**

In the event of a medical emergency the Investigator may contact [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 eCRF 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 SAEs, standard reporting timelines apply, see Section 6.3.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

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

13.3.1 Maternal exposure

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

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.

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 6.3.4, and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

13.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 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

CTCAE v4.03 2010
Common Terminology Criteria for Adverse Events Version 4.03 2010. Available from URL: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed 03 April 2013.

Food and Drug Administration 2002
United States Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry -Food-Effect Bioavailability and Fed Bioequivalence Studies. December 2002

Clinical Study Protocol Appendix A

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0816C00004
Edition Number	1
Date	[redacted]
Protocol Dated	[redacted]

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Randomised, Open-label, Three-part, Phase I Study to Determine the Effect of Food on the Pharmacokinetics of Olaparib and to Provide Data on the Effect of Olaparib on QT Interval Following Oral Dosing of a Tablet Formulation in Patients with Advanced Solid Tumours

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

[redacted]

ASTRAZENECA SIGNATURE(S)

A Randomised, Open-label, Three-part, Phase I Study to Determine the Effect of Food on the Pharmacokinetics of Olaparib and to Provide Data on the Effect of Olaparib on QT Interval Following Oral Dosing of a Tablet Formulation in Patients with Advanced Solid Tumours

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[redacted]

ASTRAZENECA SIGNATURE(S)

A Randomised, Open-label, Three-part, Phase I Study to Determine the Effect of Food on the Pharmacokinetics of Olaparib and to Provide Data on the Effect of Olaparib on QT Interval Following Oral Dosing of a Tablet Formulation in Patients with Advanced Solid Tumours

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

[redacted]

[redacted]

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A Randomised, Open-label, Three-part, Phase I Study to Determine the Effect of Food on the Pharmacokinetics of Olaparib Following Oral Dosing of a Tablet Formulation and to Provide Data on the Effect of Oral Dosing of Olaparib on QT Interval in Patients with Advanced Solid Tumours

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations, and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

[redacted]

[redacted]

Clinical Study Protocol Appendix B

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0816C00004
Edition Number	1
Date	[redacted]

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

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Clinical Study Protocol Appendix C

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0816C00004
Edition Number	1
Date	[redacted]

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

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

AstraZeneca

Clinical Study Protocol Appendix D	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0816C00004
Edition Number	1
Date	[redacted]

Appendix D
Pharmacogenetics Research – Not Applicable

AstraZeneca

Clinical Study Protocol Appendix E	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0816C00004
Edition Number	1
Date	[redacted]

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:

- 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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Clinical Study Protocol Appendix F	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0816C00004
Edition Number	1
Date	[redacted]

Appendix F
Acceptable Birth Control Methods

ACCEPTABLE BIRTH CONTROL METHODS

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

Patients of childbearing potential and their partners, who are sexually active, must agree to the use of 2 highly effective forms of contraception throughout their participation in the study and for 3 months after last dose of study drug.

Acceptable non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must be for the total duration of the trial and the drug washout period.
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion plus male condom with spermicide
- IUD plus male condom + spermicide. Provided coils are copper-banded

Acceptable hormonal methods:

- Etonogestrel implants (eg, Implanon, Norplan) + male condom with spermicide
- Normal and low dose combined oral pills + male condom with spermicide
- Norelgestromin / EE transdermal system + male condom with spermicide
- Intravaginal device + male condom with spermicide (eg, EE and etonogestrel)
- Cerazette (desogestrel) + male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.

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Clinical Study Protocol Appendix G	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0816C00004
Edition Number	1
Date	[redacted]

Appendix G
High-Fat Meal and Snack

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1. HIGH-FAT MEAL

In accordance with Food and Drug Administration (FDA) guidance (Food and Drug Administration 2002), the high fat meal should have a total of approximately 800 to 1000 kcal, with approximately 50% of the calorific content made up from fat. The meal should therefore derive approximately 150, 250 and 500 to 600 kcal from protein, carbohydrate and fat respectively, as shown in Table 1.

The exact composition of the meal may vary as long as the totals are within 5% of those detailed.

Table 1 High-fat meal (Food and Drug Administration 2002)

	Protein	**kcal**	Fat	**kcal**	Carbo-hydrate	**kcal**	Total kcal
150 mL whole milk (3% fat)	4.9	19.6	5.7	51.3	10	40	110.9
45 g of cereal (cornflakes)	3.9	15.6	0.8	5.8	15	60	81.4
½ a slice fried bread	1.5	6	10.3	92.7	10	40	138.7
60 g lean back bacon (2 rashers)	19.7	78.8	13.4	120.6			199.4
1 lightly fried egg	8.5	34	11.2	100.8			134.8
3 slices of toast	6.9	27.6	1.5	13.5	30	120	161.1
30 g of butter			16	144			144
200 mL decaf tea/coffee with milk from allowance							
Totals	45.4	**181.6**	58.9	**528.7**	65	**260**	**970.3**
% of total kcal		**19**		**54**		**27**	
FDA guidelines		**150**		**500-600**		**250**	**800-1000**

2. SNACK

If patients have signs or symptoms of hypoglycaemia after they have received olaparib in the fasted state, they may have a light snack of a piece of buttered toast or 2 plain biscuits.

3. REFERENCES

Food and Drug Administration 2002
U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry -Food-Effect Bioavailability and Fed Bioequivalence Studies. December 2002

Clinical Study Protocol Appendix H	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0816C00004
Edition Number	1
Date	[redacted]

Appendix H
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**