Clinical Study Protocol

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An Open Label, Single Arm, Multicentre Study to Assess the Clinical Effectiveness and Safety of Lynparza (Olaparib) Capsules Maintenance Monotherapy in Platinum Sensitive Relapsed somatic or germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy (ORZORA)

Sponsor: *AstraZeneca AB, 151 85 Södertälje, Sweden.*

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VERSION HISTORY

Protocol Edition Number 1, 06 February 2015
Original Version
Protocol Edition Number 2, 22 December 2015
Refer to the Clinical Study Protocol Amendment Number 1.0 for description of change with reason.
Protocol Edition Number 3, 20 July 2016
Sections: 1.1.4 Homologous recombination repair defects; 5.7.2 Collection of tumour sample for HRR testing; 5.7.4 Exploratory use of data generated from CCI [redacted] Central testing of tumour sample (Optional) **Description of change with reason**: new sections added to describe and incorporate new exploratory cohort. This exploratory cohort is comprised of patients who carry deleterious or suspected deleterious *BRCA*-independent genetic alteration in any of 13 genes involved in the Homologous Recombination Repair (HRR) pathway (HRRm cohort). The real world clinical effectiveness and safety of olaparib maintenance therapy will be described for this exploratory HRRm cohort. **Sections:** 1.2 Research hypothesis; 1.3 Rationale for study design and doses; 1.4 Benefit/risk and ethical assessment; 1.5 Study Design; Figure 1 Study Flow Chart; 3 Patient Selection, Enrolment, Restrictions, Discontinuation and Withdrawal; Figure 2 Screening Flow Chart; 5.7.1 Collection of tumour sample for BRCA testing at screening (mandatory); 5.7.3 Collection of tumour sample for exploratory analysis at screening and at disease progression (optional); 5.7.7 Guidance for BRCA and HRR testing **Description of change with reason**: updated to describe and incorporate the exploratory HRRm cohort. **Sections:** 2.4 Exploratory Objectives; 8 Statistical Considerations; 8.1 Sample Size Estimate; 8.4 Methods for statistical analyses; 8.4.1 Analysis of the primary variable; 8.4.2 Analysis of the secondary variable(s); 8.4.3 Subgroup Analysis **Description of change with reason**: added a new exploratory objective and outcome measures to include the planned exploratory research of HRRm cohort and blood samples collected for ctDNA. Updated an exploratory objective that will include analysis of HRRm cohort. Planned statistical analysis updated to incorporate the new exploratory objectives.

Section: 3.1 Inclusion criteria
Description of change with reason: updated inclusion criterion #3 to describe the inclusion criteria for inclusion into the exploratory HRRm cohort.

Section: 4 Study Plan and Timing of Procedures
Description of change with reason: Table 1 Study Schedule Screening updated to add collection of tumour sample for HRR testing. Table 2 Study Schedule – On Study Treatment and Discontinuation updated to add collection of blood samples for ctDNA analysis.

Section: 4.1 Enrolment/Screening Period
Description of change with reason: updated to include description of enrolment and screening procedures associated with addition of exploratory HRRm cohort and collection of optional blood samples for ctDNA analysis.

Section: 5.7.6 Collection of blood sample for ctDNA analysis
Description of change with reason: new section added to describe collection of blood samples for ctDNA analysis to incorporate the addition of optional blood samples collection for the exploratory ctDNA analysis.

Sections: 5.7.11 Withdrawal of Informed Consent for donated biological samples; 9.3 Ethics and Regulatory review
Description of change with reason: updated to incorporate collection of biological samples for exploratory HRRm cohort and optional blood samples for circulating tumour DNA (ctDNA) analysis.

Sections: 5.8 Blood Volume; Table 5 Estimated maximum volume of blood to be drawn from each patient based on 6 months of treatment
Description of change with reason: updated to reflect collection of optional blood samples for the ctDNA analysis.

Sections: 8.2 Definition of Analysis sets; Table 6 Summary of Outcome Variables and Analysis Populations; 8.2.1 Full analysis set; 8.2.2 Safety Analysis Set; 8.2.4 PRO Analysis

Set
Description of change with reason: corrected definitions of analysis sets to align with the intended analysis. The efficacy analysis set is replaced by the full analysis set. Updated the PRO analysis set.

Sections: Protocol Synopsis; Table of Content; List of Abbreviations; 10 List of References
Description of change with reason: updated to reflect changes in the protocol text incorporating the exploratory HRRm cohort and collection of blood samples for ctDNA analysis.

Administrative changes (e.g., correction of typos, clarification in the text) were made throughout the Protocol due to inconsistencies identified in the text.

PROTOCOL SYNOPSIS

An Open Label, Single Arm, Multicentre Study to Assess the Clinical Effectiveness and Safety of Lynparza (Olaparib) Capsules Maintenance Monotherapy in Platinum Sensitive Relapsed somatic or germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy (ORZORA)

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Study site(s) and number of patients planned

The study will be conducted in approximately 8 countries worldwide. Approximately 60 centres will be initiated to enrol up to approximately 250 patients with somatic or germline *BRCA* mutated ovarian cancer.

Patients enrolled in the study will have evidence of a deleterious or suspected deleterious germline or somatic *BRCA* mutation. In order to avoid including mainly patients with previously diagnosed germline *BRCA* mutated disease, patients previously diagnosed with germline *BRCA* (*gBRCA*) mutation will not be included in this study.

Considering the natural *BRCA* mutation prevalence in this patient population and treatment setting, it is estimated that there will be at least 50 patients with somatic *BRCA* mutated (s*BRCA*m) disease within the planned overall *BRCA* mutated patient population. Additional sites and countries may be added dependent on recruitment rates.

An additional exploratory cohort will be comprised of patients who carry a deleterious or suspected deleterious *BRCA*-independent genetic alteration in any of 13 genes involved in the Homologous Recombination Repair (HRR) pathway (HRRm cohort). HRR gene mutations will be identified using the investigational Next Generation Sequencing (NGS)-based clinical trial assay known as the "Lynparza HRR Assay" from CCI
Assuming that approximately 5% of patients with *BRCA* wild type (*BCRA*wt) disease screened in the study will carry a qualifying genetic alteration in any of the 13 genes involved in the HRR pathway (excluding *BRCA1* and *BRCA2*), it is estimated that approximately 25 patients will be included in the HRRm cohort before the target number of 250 patients with *BRCA*m disease is reached.

Study period	Timeline
Estimated date of first patient enrolled	Q2 (Q3) 2015
Estimated date of last patient enrolled	Q3 2017
Estimated date of last patient completed**	Q3 2018

** Estimated date of 150th progression free survival (PFS) event among patients with *BRCA*m disease

Study phase nomenclature will depend upon local regulatory approval status of olaparib. Pre-regulatory approval status will define ORZORA a phase IIIb study and IV study prior or post regulatory approval accordingly. Importantly, these differences do not affect study methodology. However the potential need for local regulatory or other agency notification should be determined for individual countries.

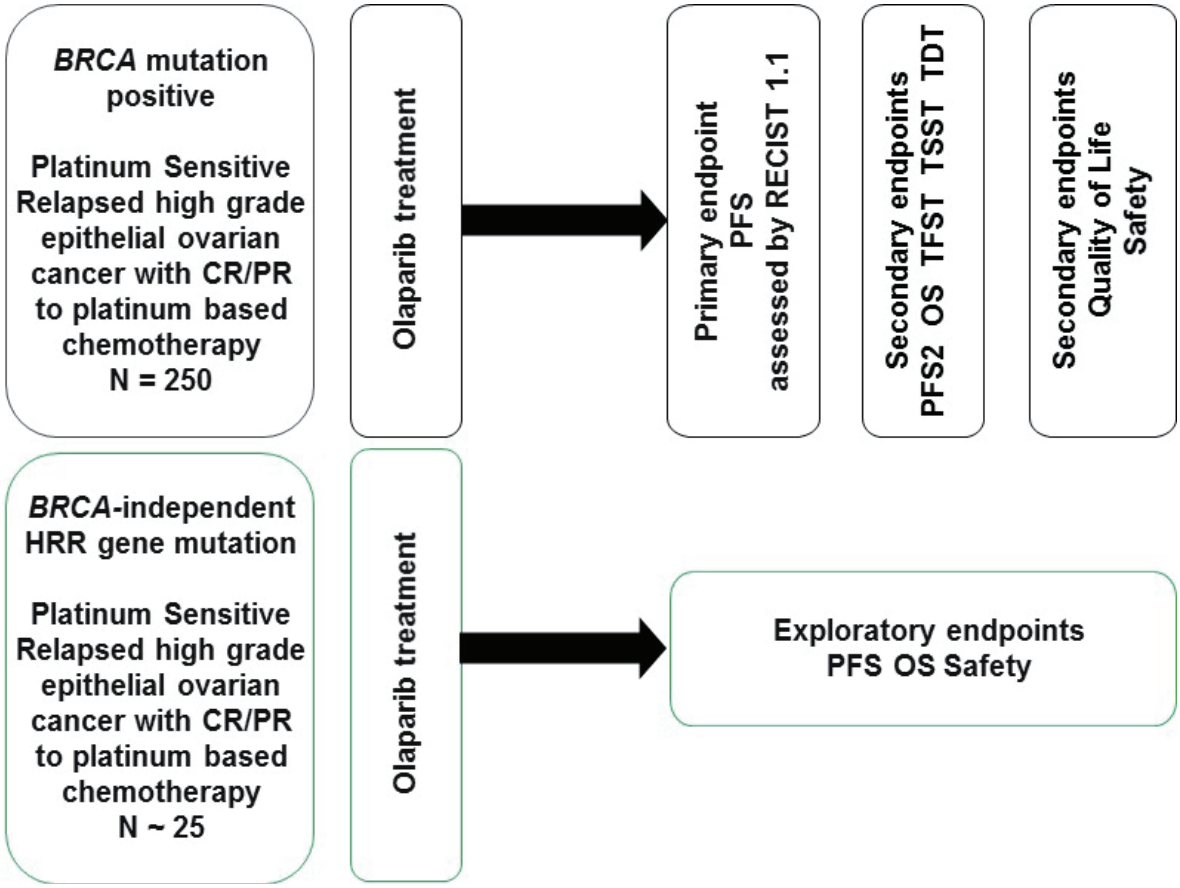
Study design

This is a prospective, open-label, single arm, multi-centre study to assess the clinical effectiveness and safety of olaparib maintenance monotherapy and will be conducted in line with the European Union (EU) approved prescribing information and indication in patients with platinum sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

BRCA mutations are documented germline or somatic mutations in *BRCA1* or *BRCA2* that are predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function).

An additional, exploratory cohort of patients with *BRCA*-independent qualifying alterations in genes involved in the HRR pathway will be enrolled into the study (HRRm cohort). Qualifying genetic alterations are loss of function (LOF) mutations in any of the 13 genes other than *BRCA1* and *BRCA2* involved in the HRR pathway that are predicted to be deleterious or suspected deleterious. These 13 genes are: *ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*. The investigational clinical trial assay known as the Lynparza HRR Assay from CCI will be used for this testing.

Figure 1 Study Flow Chart



Patients will be assigned olaparib capsules p.o. 400 mg twice daily. They should initiate olaparib treatment within 8 weeks after their last dose of platinum-containing chemotherapy (last dose is the day of the last infusion).

All patients will have clinical and objective radiological tumour assessments according to modified Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 at baseline and every 12 weeks relative to date of enrolment, until objective radiological disease progression as determined by the investigator. Patients could continue to receive olaparib for as long as determined by the investigator, until objective radiological disease progression or as long as in the investigator's opinion they are benefiting from treatment in relation to other clinical assessments and they do not meet any other discontinuation criteria. The study will recruit at least 50 patients with s*BRCA*m disease. Once a patient has discontinued olaparib she will be managed as per local clinical practice but will remain in the study and data will be collected on subsequent treatments, progression, overall survival and safety.

Objectives

Co-Primary Objectives:	Outcome Measure:
• To assess the real world clinical effectiveness of olaparib maintenance monotherapy by investigator assessed progression free survival (PFS) according to modified Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 in patients with s*BRCA*m ovarian cancer. • To assess the real world clinical effectiveness of olaparib maintenance monotherapy by investigator assessed PFS according to RECIST 1.1 in patients with *BRCA*m ovarian cancer.	Time from study enrolment to disease progression (assessed according to RECIST 1.1 guidelines) or death.

Secondary Objectives:	**Outcome Measure:**
To assess the real world clinical effectiveness of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer, by assessment of: a) overall survival (OS), b) time to investigator-assessed second progression (PFS2), or death.	a) Time to death b) Time to second progression event or death if this occurs before second progression event.
To assess the real world clinical effectiveness of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer, by assessment of a) time to first subsequent therapy or death (TFST), b) time to second subsequent therapy or death (TSST) and, c) time to olaparib discontinuation or death (TDT).	a) Time to first subsequent treatment commencement or death if this occurs before commencement of first subsequent treatment b) Time to second subsequent treatment commencement or death if this occurs before commencement of second subsequent treatment c) Time to olaparib discontinuation or death if this occurs before discontinuation of olaparib maintenance therapy.
To assess and describe the quality of life (QoL) of patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer.	Functional Assessment of Cancer Therapy-Ovarian (FACT-O), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, and ORZORA QoL Additional Items Questionnaire
To describe patterns of routine clinical use of olaparib, the nature and patterns of adverse events (AEs) of nausea and vomiting and their impact on QoL in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer. To describe nausea/vomiting toxicity management patterns used in routine clinical practice.	Safety summary tables, Functional Living Index-Emesis (FLIE) Questionnaire, and concomitant medication use.

Safety Objective:	**Outcome Measure:**
To assess the safety and tolerability of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer.	AEs/Serious adverse events (SAEs)/AE of special interest (AESI)

Exploratory Objectives:	**Outcome Measure:**
To describe the longer term safety of olaparib monotherapy, including follow up for Myelodysplastic Syndrome (MDS)/ Acute Myeloid Leukaemia (AML)/ and New primary malignancies (other than MDS/AML).	Collection of long term adverse events, including MDS/ AML or new primary malignancies
To correlate the incidence of side effects and QoL according to age and the presence of comorbidities.	Based on collected and summarised outcomes and comorbidities
To describe the clinical effectiveness of (response to) subsequent line of treatment and correlating it with the progression-free interval (PFI) (artificial prolongation of PFI through olaparib).	Description of maximum response to subsequent line of treatment
To describe the efficacy of olaparib according to the previous therapy, with or without bevacizumab, and according to the PFI (recurrence during or after the end of bevacizumab maintenance).	Based on collected and summarised outcomes
To describe the activity of olaparib according to the germline mutational status (*BRCA1* vs *BRCA2*), and to the presence of family history (yes vs no).	Based on collected and summarised outcomes and family history
To describe the kinetic of CA-125 progression according to Gynecological Cancer InterGroup (GCIG) criteria and its correlation with disease progression by RECIST 1.1 guidelines during olaparib therapy.	Based on collected and summarised outcomes
To measure loss of heterozygosity (LOH) for the *BRCA1* and *BRCA2* genes in tumour samples and explore any potential association with efficacy.	Based on all available tumour samples collected and summarised outcomes.

Exploratory Objectives:	**Outcome Measure:**
To describe the real world clinical effectiveness and safety of olaparib maintenance monotherapy in patients with *BRCA*-independent HRRm ovarian cancer, by the following: • Investigator assessed PFS according to RECIST 1.1 • OS • Safety and tolerability.	a) Time from study enrolment to disease progression (assessed according to RECIST 1.1 guidelines) or death b) Time to death c) AEs, SAEs, AESI
Potential exploratory research into frequency, nature and predictive value of HRR gene mutations, including *BRCA1* and *BRCA2*, may be performed on the optional collected and stored tumour samples available at study entry or tumour biopsy samples collected during the course of the study. These could include studying resistance mechanisms to olaparib, future exploratory research into factors that may influence development of cancer and/or response to study treatment. To collect and store deoxyribonucleic acid (DNA) (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response to study treatment and or susceptibility to disease (optional)*.	
To explore the feasibility of reliably measuring s*BRCA*m and HRRm from circulating tumour DNA (ctDNA)*	

* These exploratory analyses may not be reported in the clinical study report (CSR), if not they will be reported separately.

Target patient population

Eligible patients will be those with platinum sensitive relapsed (PSR) high grade epithelial ovarian cancer, primary peritoneal and/or fallopian tube cancer who are found to carry a germline or somatic *BRCA* mutation known or suspected to be deleterious.

Patients must have completed at least 2 previous lines of platinum-based therapy (e.g., containing carboplatin or cisplatin) before entry to the study and must be considered platinum sensitive after the penultimate platinum-based chemotherapy. Eligible patients must be in

complete or partial response following platinum-based chemotherapy prior to enrolment in the study.

Only patients with unknown germline *BRCA* mutation status or patients found to carry germline *BRCA* wild type (g*BRCA*wt) disease or patients previously identified as having *BRCA*m disease based on a tumour test (with unknown g*BRCA* or with previously identified g*BRCA*wt status) will be considered for screening. Patients previously diagnosed with g*BRCA*m disease will not be included in this study. *BRCA* mutation status will be determined or confirmed through central blood and tumour testing (as outlined in Section 5.7.6).

Exploratory patient population

Patients screened for the study with unknown *BRCA* status or with known g*BRCA*wt status for whom an adequate archival tumour tissue sample is available will be tested for qualifying HRR gene alterations.

Patients found not to carry a *BRCA* mutation in their tumour (tumour *BRCA*wt), and with qualifying *BRCA*-independent HRR genetic alterations will be included in the study (HRRm cohort), and analysed as a separate exploratory cohort.

Duration of treatment

Patients should continue to receive olaparib until objective radiological disease progression according to RECIST 1.1 guidelines as assessed by the investigator or as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 3.9. Once patients have been discontinued from olaparib, other treatment options will be at the discretion of the investigator.

Investigational product, dosage and mode of administration

Olaparib will be available as the capsule formulation as follows:

- Capsules containing 50 mg olaparib. Patients will be administered olaparib orally at a dose of 400 mg twice daily (bid), equivalent to a total daily dose of 800 mg. The planned dose of 400 mg bid will be made up of eight 50 mg capsules bid.

Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea, and anaemia and dose reduction can be considered. For more information please refer to Section 6.8 and the prescribing information (Appendix G) or to the investigator's brochure as appropriate.

Statistical methods

No formal sample size calculation is provided for this study. The sample size of approximately 250 patients with *BRCA* mutated ovarian cancer is driven by the need to have at least 50 patients with s*BRCA*m disease, and an adequate number of patients across participating countries to allow for individual country and/or regional summaries and to help

understand patterns of olaparib use in routine clinical practice across multiple countries with the capsule formulation and across various subgroups.

Assuming that approximately 5% of patients with *BRCA*wt disease screened in the study will carry a qualifying genetic alteration in any of the 13 genes involved in the HRR pathway (i.e., *BRCA*-independent HRRm), it is expected that approximately 25 patients will be included in the HRRm cohort before the target number of 250 patients with *BRCA*m disease is reached.

Patients enrolled with s*BRCA*m disease

Assuming a median PFS value of 11.2 months (as observed in the phase 2 maintenance study), and a data cut off at 60% maturity, 30 progression or death events are expected from 50 patients. Assuming 23 months non-linear recruitment in the s*BRCA*m cohort, these 30 progression or death events are expected to occur approximately 32 months after first subject is enrolled in the study (FSI).

All *BRCA*m patients

Data will be summarised for all patients who have received at least one dose of olaparib. The sample size of approximately 250 patients is driven by the need to understand patterns of olaparib use across multiple countries with the capsule formulation and across various subgroups and the primary analysis will be performed after the accumulation of 150 progression or death events which corresponds to 60% maturity. Assuming a median PFS value of 11.2 months and a data cut off at 60% maturity with approximately 23 months of non-linear recruitment 150 progression or death events are expected to occur approximately 32 months after first subject is enrolled in the study (FSI).

PFS will be presented as a median and 95% confidence interval, with no formal statistical comparison between patients with s*BRCA*m or g*BRCA*m disease as the single-arm design of this study prevents the identification of prognostic or predictive factors.

Subgroups will be presented, including patients with g*BRCA*m disease, mutation type (*BRCA1*, or *BRCA2* or both), and prior and subsequent Poly-adenosine 5'diphosphoribose (ADP) Polymerase (PARP) inhibitor use.

All time to event endpoints will be described as for PFS. A summary of PFS2 and OS will be produced at the time of the PFS data cut off. QoL and safety data will be summarised. For more information please refer to Section 8.

Patients enrolled with HRRm disease

The analyses of PFS, OS and safety data will be repeated for the exploratory cohort of patients with *BRCA*-independent HRRm ovarian cancer.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACMG	American College of Medical Genetics and Genomics
AE	Adverse Event (see definition in Section 6.1)
AESI	Adverse Event of Special Interest (see Section 6.3)
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukaemia
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
Bid	Twice a day
BP	Blood Pressure
BRAC*Analysis*®	Gene sequencing and large rearrangement analysis for Hereditary Breast and Ovarian Cancer, registered trademark of Myriad Genetics, Inc.
BRCA	Breast cancer susceptibility gene (in accordance with scientific convention, gene and mutation is italicised whereas protein is not italicised)
*BRCA*m	*gBRCA* and/or *sBRCA* mutated
*BRCA*wt	*gBRCA* and/or *sBRCA* wild type
BUN	Blood Urea Nitrogen
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating Tumour DNA
DAE	Discontinuation of Investigational Product due to Adverse Event

Abbreviation or special term	Explanation
DCO	Data Cut-Off
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
DSB	Double Strand Break
DUS	Disease Under Study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	electronic Case Report Form
ENGOT	European Network of Gynaecological Oncological Trial Groups
EU	European Union
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-O	Functional Assessment of Cancer Therapy-Ovarian
FAS	Full Analysis Set
FFPE	Formalin-Fixed, Paraffin-Embedded
FLIE	Functional Living Index-Emesis
CCI [redacted]	
FSI	First Subject In (enrolled)
g*BRCA*	germline *BRCA*
g*BRCA*m	germline *BRCA* mutated
g*BRCA*wt	Germline *BRCA* wild type
GCIG	Gynecological Cancer InterGroup
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRD	Homologous Recombination Deficiency
HRQoL	Health-Related Quality of Life
HRR	Homologous Recombination Repair
HRRm	Qualifying mutation in the tumour of any of 15 genes involved in DNA homologous recombination repair
HRT	Hormone Replacement Therapy

Abbreviation or special term	Explanation
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
INR	International Normalised Ratio
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally.
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan Meier
LOF	Loss of Function
LOH	Loss of Heterozygosity
MCV	Mean Cell Volume
MDS	Myelodysplastic Syndrome
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NE	Not Evaluable
NGS	Next Generation Sequencing
NTL	Non-Target Lesion
OAE	Other Significant Adverse Event (see definition in Section 8.3.6)
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly-adenosine 5'diphosphoribose (ADP) Polymerase / Polymerisation
PD	Progression of Disease
PFI	Progression-Free Interval
PFS	Progression Free Survival during initial olaparib maintenance therapy
PFS2	Progression Free Survival following initial olaparib maintenance and subsequent chemotherapy
PI	Principal Investigator
p.o.	Administered by mouth
PR	Partial Response
PRO	Patient Reported Outcome

Abbreviation or special term	Explanation
PSR	Platinum Sensitive Relapsed
QoL	Quality of Life
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event (see definition in Section 6.2)
SAP	Statistical Analysis Plan
s*BRCA*m	Somatic tumour *BRCA* mutated (mutation detected in the tumour but not in the germline)
*sBRCA*wt	Somatic tumour *BRCA* wild type
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvate Transaminase
SSB	Single Strand Breaks
TDT	Time to Discontinuation of Treatment or Death
TFST	Time to First Subsequent Therapy (Treatment) or Death
TL	Target Lesion
TOI	Trial Outcome Index
TSST	Time to Second Subsequent Therapy (Treatment) or Death
ULN	Upper Limit of Normal
US	United States
WBDC	Web Based Data Capture
wt	Wild type. Patients without evidence of *BRCA 1* or *BRCA 2* deleterious or suspected deleterious mutations for a given gene or set of genes (e.g. *BRCA 1* or *BRCA 2*)

1. INTRODUCTION

1.1 Background

1.1.1 Ovarian cancer and its treatment

Ovarian cancer is the fifth most common cause of death from cancer in women (Colombo et al 2010; NCCN Clinical Practice Guidelines in Oncology 2013). In the European Community, approximately 28,000 new cases of ovarian cancer and approximately 17,000 deaths are reported annually, ranking ovarian cancer as the leading cause of death from gynaecological cancer. The incidence rates of ovarian cancer increase with age and are highest in the eighth decade of life (50.8/100,000 and 50.3/100,000 in age groups 80-84 and 85+, respectively)
(Howlader et al 2014). In the United States (US), nearly 80% of the patients are diagnosed with advanced disease (regional or distant), while only 15% are diagnosed at the localized stage (Howlader et al 2014). Approximately 44% of women diagnosed with ovarian cancer (at any stage) survive 5 years from diagnosis, while among those diagnosed at the distant stage of the disease 5-year survival is ~27% (Siegel et al 2014). In Europe, an average 5-year relative survival (~42%) is similar to that found in the US (Sant et al 2009).

The standard therapy for advanced ovarian cancer consists of radical debulking surgery followed by post-operative platinum-based first-line chemotherapy. Since 1996, platinum and paclitaxel combination therapy has become the standard-of-care first-line chemotherapy regimen (McGuire et al 1996). Worldwide, the use of carboplatin has replaced that of cisplatin because of carboplatin's superior tolerability profile together with equal effectiveness. However, the success of this approach is limited and approximately 70% of patients fail to achieve complete responses, or eventually relapse, after a varying disease-free interval.

Should a relapse or a progression after first-line therapy occur, cure of the disease is rarely possible. In these cases, second-line chemotherapy is usually offered, with a palliative intent. Recurrence-free interval influences the choice of possible second-line chemotherapy, specifically the value of platinum re-exposure (Blackledge et al 1989, Gore et al 1990, Markman et al 1991) and is of prognostic importance for the ongoing course of the illness (Eisenhauer et al 1997). Patients with ovarian cancer who developed recurrence >6 months after completion of first line platinum chemotherapy are characterised as having platinum sensitive disease.

For patients with platinum sensitive disease, response rates of 20% to 30% may be seen with platinum re-treatment in those with a platinum-free interval of 6 to 12 months. In those patients with treatment-free intervals of >12 months, response rates in the range of 30% to 70% may be seen, and some patients may benefit from durable second remissions. Carboplatin in combination with gemcitabine, pegylated liposomal doxorubicin or paclitaxel represents the main treatment options for patients with relapsed platinum sensitive disease, being repeated as long as the patients remain platinum sensitive.

1.1.2 *BRCA* mutation positive ovarian cancer

An important risk factor for ovarian cancer is genetic predisposition with *BRCA1* or *BRCA2* mutations (i.e., germline *BRCA* mutated [g*BRCA*m]) which account for the majority of hereditary ovarian cancers. If a lifetime risk for ovarian cancer among women in the general population is estimated to be 1.4 percent (14 out of 1,000), a woman with *BRCA*1 or *BRCA*2 deleterious mutation has a lifetime risk of 15 to 40 percent (150–400 out of 1,000) (NCI; *BRCA*1 and *BRCA*2: Cancer Risk and Genetic Testing). *BRCA* mutated ovarian cancer patients can also develop ovarian cancer earlier in their life than those without the mutation. Deficiency in *BRCA* function is thought to arise when the relevant second copy of the gene is lost (loss of heterozygosity) in tumorigenesis (George et al 2014).

If all ovarian cancer patients underwent germline *BRCA* (g*BRCA*) testing, current estimates indicate that 13% to 14% of the overall ovarian cancer population would have g*BRCA1/2* mutations (Alsop et al 2012, Zhang et al 2011), and the proportion of patients with g*BRCA* mutations may be as high as 22% in patients with high grade epithelial ovarian cancer. In addition, a population of ovarian cancer patients whose tumours harbour *BRCA1* and *BRCA2* mutations that are not detected in the germline (~7% of unselected patients) also exist and are defined as somatic *BRCA* mutations (s*BRCA*m) (Hennessy et al 2010). Based on the above overall incidence of g*BRCA* and s*BRCA* mutations reported separately, it would be expected that about 30% of patients with BRCA mutated (*BRCA*m) disease overall have a somatic mutation.

Ovarian cancer patients with *BRCA* mutated disease seem to have a better prognosis compared with the overall relapsed ovarian cancer patient population but the pattern of disease is similar, with patients eventually dying from their disease. Patients with *BRCA* mutation represent a small, well defined and medically recognised subpopulation.

Throughout the protocol the term '*BRCA* mutation' is used to refer to a *BRCA1* or *BRCA2* mutation (detected either in the germline or in the tumour) classified as 'deleterious' or 'suspected deleterious' in accordance with the American College of Medical Genetics and Genomics (ACMG) recommendations for standards for interpretation and reporting of sequence variants (Richards et al 2008).

Where reference is made to germline *BRCA* mutations specifically, the abbreviation *gBRCA*m is used. Where reference is made to patients who harbour a tumour *BRCA* mutation but are known not to harbour a germline *BRCA* mutation, the abbreviation *sBRCA*m is used to indicate a somatic tumour *BRCA* mutation. In addition, mutated or wild type (wt) may be designated by *BRCA*m and *BRCA*wt, respectively. Patients are classified as *BRCA* mutated by virtue of having *BRCA* mutated status in either their blood or tumour sample.

1.1.3 PARP inhibition as a target for *BRCA* mutation positive ovarian cancer

Investigators should be familiar with the current olaparib (AZD2281, KU-0059436) Investigator's Brochure (IB) or Prescribing Information (Appendix G) as applicable depending on country specific marketing authorisation status.

Olaparib 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 (HRR). Tumours with homologous recombination deficiencies (HRD), such as ovarian cancers in patients with *BRCA* 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.

BRCA1 and *BRCA2* defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo (Rottenberg et al 2008, Hay et al 2009) and in the clinic (Fong et al 2009). The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair (Helleday 2011; Murai et al 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HRR. 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.

The phase II study D0810C00019 was a randomised, double-blind, placebo-controlled study to evaluate maintenance treatment with olaparib (capsule formulation) in patients with platinum sensitive relapsed high grade epithelial ovarian cancer who had received ≥2 previous platinum regimens and were in partial or complete response following their last platinum-containing regimen. The primary endpoint was investigator-assessed progression free survival (PFS).

In total, 265 patients were randomised to olaparib 400 mg bid (136) or placebo (129). The primary analysis was carried out following 154 PFS events and demonstrated that maintenance treatment with olaparib led to a significant PFS improvement vs placebo (hazard ratio [HR] 0.35; 95% confidence interval [CI] 0.25-0.49; p<0.00001) (Ledermann et al 2012). A subgroup analysis (pre-specified in the statistical analysis plan [SAP]) suggested that olaparib may lead to a greater clinical benefit in patients with a known g*BRCA*m status was determined retrospectively for all consenting patients (n=166) using blood samples taken before randomisation. Tumour *BRCA*m status was determined from archival tumour samples of 196 patients. Since germline *BRCA* wild type (g*BRCA*wt) patients may develop somatic tumour *BRCA* mutations, efficacy analyses were performed by known g*BRCA* mutation status and known total *BRCA* mutation status. g*BRCA*m patients had the greatest PFS benefit with olaparib maintenance vs placebo (HR, 0.17; 95% CI 0.09-0.31; median: 11.2 vs 4.1 months;

p<0.001). The PFS benefit was consistent when s*BRCA*m ovarian cancers (18 patients with s*BRCA*m disease) were included to reach an overall sample of 136 patients with *BRCA*m disease (HR, 0.18; 95% CI 0.11-0.31; median: 11.2 vs 4.3 months; p<0.0001). In an interim analysis of overall survival (OS; 58% maturity), OS HRs from the g*BRCA*m subgroup was 0.85; 30% g*BRCA*m placebo patients received a subsequent PARP inhibitor. The analysis of all *BRCA*m patients was less confounded and resulted in an OS HR of 0.73 (95% CI 0.45-1.17; median: 34.9 vs 31.9 months; p=0.19). Olaparib tolerability was similar in *BRCA*m patients and the overall population.

1.1.4 Homologous recombination repair defects

As described above, PARP inhibition induces synthetic lethality in tumour cells with HRR deficiencies, such as *BRCA1/2* mutations (*BRCA*m). PARP inhibitors may also induce lethality in tumour cells that have *BRCA1/2*-unrelated deficiencies in the DNA damage repair mechanism. *BRCA*-independent defects include loss-of-function (LOF) mutations in other genes that encode proteins involved in DNA damage repair by HRR (HRRm).

AstraZeneca has partnered with CCI to develop a novel tumour tissue-based companion diagnostic – the clinical trial assay known as "Lynparza HRR Assay" – for the detection of mutations in a set of 15 HRR genes including *BRCA1, BRCA2*, and 13 other genes (*ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L*).The Lynparza HRR Assay is based on the clinical-grade next generation sequencing (NGS) CCI cancer gene-profiling test, which analyses the coding sequence of 310 cancer-related genes plus select introns from 35 genes for variants and/or rearrangements.

A patient is classified "positive" (i.e., HRRm) if any deleterious or suspected deleterious genetic alteration is found in the 13 HRR genes, other than *BRCA*1 and *BRCA*2 (i.e., *BRCA*-independent HRRm). Classification of genetic alterations is in accordance with the American College of Medical Genetics and Genomic standards and guidelines for the interpretation of sequence variants (Richards et al 2015). A genetic alteration is regarded as deleterious if it results in protein truncation (which includes nonsense, frameshift, or consensus splice site mutations), or select missense mutations well known to be deleterious in ClinVar/BIC databases. Furthermore, larger scale genetic alterations such as genomic truncating rearrangements or homozygous deletions will also be classified as "positive". Patients that do not meet such criteria are labelled as biomarker "negative".

Tumour samples from *BRCA*wt patients participating in Study D0810C00019 were analysed to determine the presence of exploratory, candidate biomarkers of sensitivity to olaparib. Of the 95 *BRCA*wt patients for whom comprehensive NGS tumour profiling was completed, 21 patients (22%) had at least one LOF mutation in a candidate HRR gene (*BRCA*wt HRRm subset); however, analyses of PFS, OS, time to first and second subsequent therapy have not been performed for *BRCA*-independent HRRm patients because there were insufficient events in this patient subset. Further clinical studies are needed to fully characterize the activity of olaparib in patients with a HRRm pattern (Hodgson et al 2015).

Furthermore, in the phase II Trial of PARP Inhibition in Prostate Cancer, in patients with metastatic castration-resistant prostate cancer no longer responding to standard treatments, 16 of 49 patients presented genetic alterations in the HRR pathway. Of these 16 patients, 14 patients (88%) had a response to olaparib (Mateo et al 2015).

1.1.5 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the olaparib Investigational Brochure (IB) and the Prescribing Information (Appendix G) as applicable depending on country specific marketing authorisation status.

1.1.6 Toxicology and safety pharmacology summary

Olaparib has been tested in a standard range of safety pharmacology studies e.g., 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 and the Prescribing Information (Appendix G) as applicable depending on country specific marketing authorisation status.

1.1.7 Clinical experience

Clinical experience with olaparib is fully described in the current version of the olaparib IB and the Prescribing Information (Appendix G) as applicable depending on country specific marketing authorisation status.

1.2 Research hypothesis

Olaparib administered as monotherapy as a treatment in routine clinical practice in the maintenance setting in line with the approved indication in the European Union (EU) exhibits the level of clinical effectiveness, safety and tolerability that are consistent with those seen in controlled clinical trials to date within the olaparib clinical development programme in the same treatment setting. Patients with somatic *BRCA* deleterious or suspected deleterious mutated disease (s*BRCA*m) appear to have consistent outcomes with those reported previously

in patients with g*BRCA*m ovarian cancer. The capsule formulation is appropriate to use in this clinical setting in patients with *BRCA* mutated relapsed ovarian cancer who have a complete or partial response to platinum-based chemotherapy.

The exploratory HRRm cohort will assess olaparib activity among patients with ovarian cancer who carry LOF genetic alterations among 13 genes, other than *BRCA1* and *BRCA2* (i.e., *BRCA*-independent HRRm), involved in the HRR pathway, as identified on an archival tumour sample by the Lynparza HRR Assay (see Section 1.1.4).

1.3 Rationale for study design and doses

Based on the results of a pivotal phase II trial (D0810C00019), described in more detail above (Section 1.1.3), olaparib as the capsule formulation at a daily recommended dose of 400 mg twice daily (a total daily dose of 800 mg) has been approved in EU as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed (PSR) *BRCA* mutated (germline and/or somatic) high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

AstraZeneca in cooperation with the European Network of Gynaecological Oncological Trial Groups (ENGOT) is also conducting currently a phase III trial (D0816C00002) to confirm the outcomes of olaparib as maintenance monotherapy in patients with PSR *BRCA* mutation positive ovarian cancer. The phase III confirmatory trial is being conducted with the new tablet formulation.

The phase II study D0810C000019 demonstrated the efficacy of olaparib maintenance when using the capsule formulation (8 capsules twice daily). A more patient friendly tablet formulation (2 tablets twice daily) has been developed and currently studied in a phase III ongoing study investigating the efficacy of the tablet formulation when given as a maintenance therapy to patients with *BRCA* mutated platinum sensitive relapsed ovarian cancer.

Further information is provided in the IB or the Prescribing Information (Appendix G) as applicable depending on country specific marketing authorisation status.

The findings from study D0810C00019 are supported by clinical data from over 350 additional patients with *BRCA*m ovarian cancer in 6 other olaparib trials demonstrating consistent response rates. Details are available in the IB and the Prescribing Information (Appendix G) as applicable depending on country specific marketing authorisation status.

The current study will allow patients to complete their platinum-containing regimen prior to enrolment and then initiate maintenance treatment with olaparib as per the EU approved indication and according to normal clinical practice. This study is the first study to explore the use of olaparib in a clinical setting very near to expected routine clinical practice and to provide valuable further insight into patients' benefit and tolerability, quality of life and clinical management in this treatment setting.

In order to avoid including mainly patients with previously diagnosed g*BRCA* mutated disease, only patients with unknown germline *BRCA* mutation status or patients found to carry g*BRCA*wt disease or patients previously identified as having *BRCA*m disease based on a tumour test (with unknown g*BRCA* mutation status or with previously identified g*BRCA*wt status) will be considered for screening. Patients previously diagnosed with g*BRCA*m disease will not be included in this study.

The study will explore whether patients presenting with *BRCA*-independent qualifying alterations in any of the 13 HRR genes tested by the Lynparza HRR Assay (HRRm exploratory cohort) may benefit from treatment with olaparib, using the same maintenance treatment regimen as approved by the European Medicines Agency for patients with s*BRCA*m or g*BRCA*m ovarian cancer.

1.4 Benefit/risk and ethical assessment

Olaparib is considered to have a positive benefit-risk profile in this study target population of relapsed *BRCA* mutated platinum sensitive ovarian cancer patients based on the randomised phase II data in the same patient population (see Section 1.3) demonstrating a large and clinically meaningful prolongation of progression free survival, with an acceptable tolerability profile for use in the maintenance setting. Platinum-containing therapy is considered the treatment of choice for patients with recurrent platinum sensitive ovarian cancer, including those patients with *BRCA*m ovarian cancer, however the duration of response (DoR) and the prolongation of the progression free interval are usually brief and these chemotherapy regimens cannot be continued until progression as they are associated with neurological, renal and haematological toxicity and cannot generally be tolerated for more than about 6 cycles. Since chemotherapy is not a viable treatment option in the maintenance setting, there is a need for a well-tolerated maintenance treatment (following completion of chemotherapy) that can be taken until disease progression to extend the progression free interval in this patient population.

Patients with *BRCA*m ovarian cancer, however, represent a targeted and clinically identifiable subpopulation.

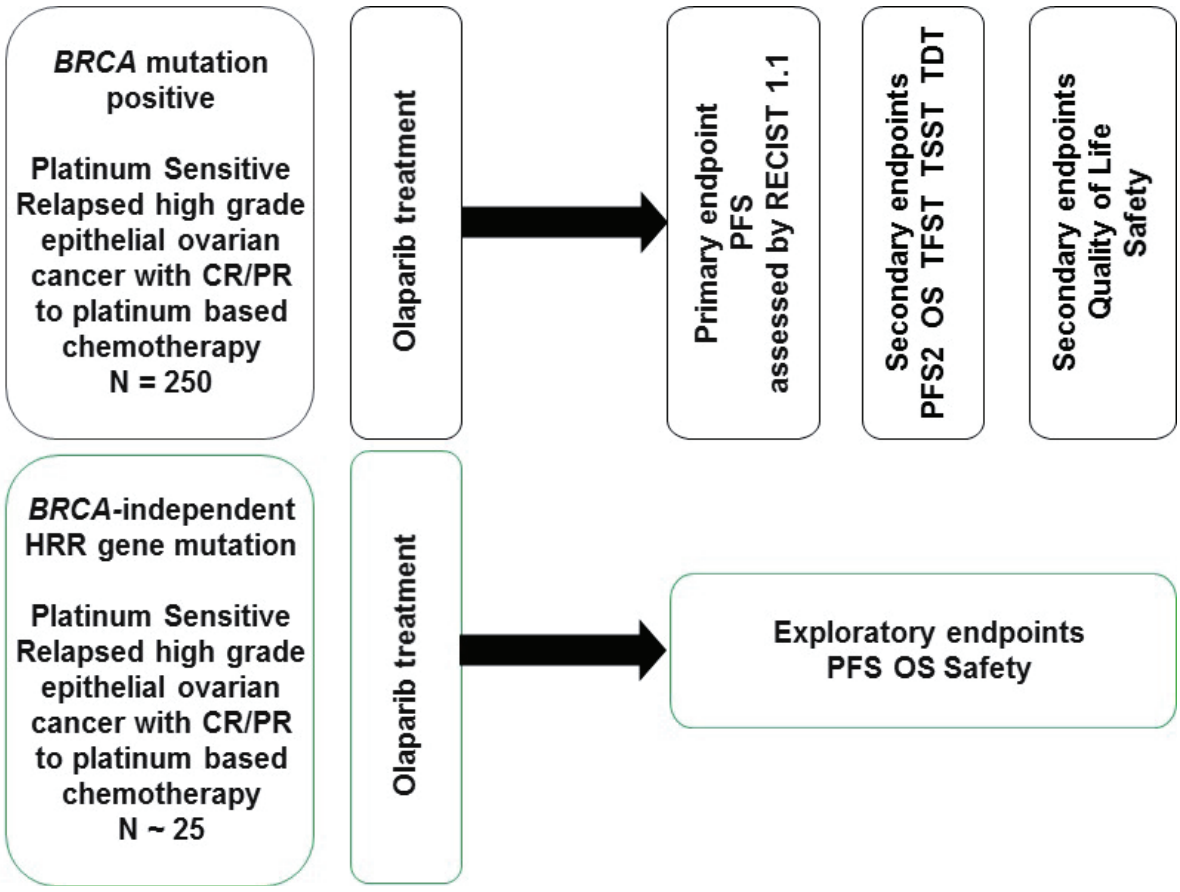
The current study design will allow patients to complete their standard platinum-containing regimen prior to enrolment and then initiate maintenance treatment with olaparib as per its EU-approved indication and according to normal clinical practice. Considering that ovarian cancer is the leading cause of death from gynaecological tumours in the Western world, the clinically meaningful efficacy benefit of olaparib in the targeted *BRCA* mutated patient population and the known tolerability profile of olaparib monotherapy used according to EU-approved indication and restrictions, the current study is considered to have a positive benefit-risk profile. Refer to the current IB or the Prescribing Information (Appendix G) as applicable depending on country specific marketing authorisation status for a complete description of the safety and tolerability profile.

An additional exploratory patient cohort will be enrolled in the study, comprised of patients with *BRCA*wt status, and *BRCA*-independent HRRm ovarian cancer. These patients will be treated and followed up in the same manner as patients with s*BRCA*m and g*BRCA*m disease.

1.5 Study Design

This is a prospective, open-label, single arm, multi-centre study to assess the real world clinical effectiveness and safety of olaparib maintenance monotherapy as the capsule formulation in relapsed high grade epithelial ovarian cancer patients (including patients with primary peritoneal and / or fallopian tube cancer) who carry germline or somatic *BRCA* mutations (documented mutation in *BRCA1* or *BRCA2* that is predicted to be deleterious or suspected deleterious [known or predicted to be detrimental/lead to loss of function]) who have responded following platinum based chemotherapy.

Figure 1 Study Flow Chart



Patients will be assigned to olaparib capsules p.o. 400 mg twice daily. They should initiate olaparib treatment within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion).

All patients will have clinical and objective radiological tumour assessments according to modified Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 guidelines at baseline and every 12 weeks relative to date of enrolment, until objective radiological disease progression as determined by the investigator. Patients could continue to receive olaparib for as long as determined by the investigator, until objective radiological disease progression or as long as in the investigator's opinion they are benefiting from treatment in relation to other clinical assessments and they do not meet any other discontinuation criteria.

The study will recruit approximately 250 patients with s*BRCA*m disease or g*BRCA*m disease, with aim to accrue a minimum of 50 patients with s*BRCA*m disease. Patients found or known to carry a deleterious or suspected deleterious mutation in the tumour will be eligible to continue study screening procedures. They will provide a blood sample to determine their mutated or wild type germline *BRCA* status (in the latter case, confirming a somatic mutation). *BRCA* mutated disease will be determined or confirmed through central blood and tumour testing (as outlined in Section 5.7.6).

Any counselling procedures required before such testing will be carried out in accordance with local hospital practice. For more information please see Section 5.7.6.

Based on the respective frequencies of g*BRCA* and s*BRCA* mutations in patients with ovarian cancers, it is expected that approximately 25% of the patients eligible to enter the study with *BRCA* mutated disease will harbour a somatic mutation. The recruitment of patients with g*BRCA*m disease may be capped if, after enrolling 150 patients onto the study, less than 50 patients are confirmed to have s*BRCA*m disease.

Additionally, an exploratory cohort of patients with tumour *BRCA*wt status, who are found to carry one or more *BRCA*-independent qualifying genetic alterations in the 13 HRR genes tested by the Lynparza HRR Assay will be enrolled in the study (HRRm cohort). It is expected that approximately 450 patients with tumour *BRCA*wt status will be screened using the Lynparza HRR Assay and approximately 5% of those screened will be enrolled into the study based on presence of *BRCA*-independent qualifying HRR mutation. Recruitment into this HRRm cohort will not interfere with the planned recruitment of approximately 250 patients with *BRCA*m ovarian cancer.

Once a patient has discontinued olaparib she will be managed as per local clinical practice but will remain in the study and data will be collected on subsequent treatments, progression and survival.

2. STUDY OBJECTIVES

2.1 Primary objectives

Co-Primary Objectives:	Outcome Measure:
• To assess the real world clinical effectiveness of olaparib maintenance monotherapy by investigator assessed progression free survival (PFS) according to modified Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 in patients with s*BRCA*m ovarian cancer. • To assess the real world clinical effectiveness of olaparib maintenance monotherapy by investigator assessed PFS according to RECIST 1.1 in patients with *BRCA*m ovarian cancer	Time from study enrolment to disease progression (assessed according to RECIST 1.1 guidelines) or death.

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To assess the real world clinical effectiveness of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer, by assessment of: a) overall survival (OS), b) time to investigator-assessed second progression (PFS2), or death.	a) Time to death b) Time to second progression event or of death if this occurs before second progression event.
To assess the real word clinical effectiveness of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer, by assessment of a) time to first subsequent therapy or death (TFST), b) time to second subsequent therapy or death (TSST) and, c) time to olaparib discontinuation or death (TDT).	a) Time to first subsequent treatment commencement or death if this occurs before commencement of first subsequent treatment b) Time to second subsequent treatment commencement or death if this occurs before commencement of second subsequent treatment c) Time to olaparib discontinuation or death if this occurs before discontinuation of olaparib maintenance therapy.

Secondary Objective:	**Outcome Measure:**
To assess and describe the quality of life (QoL) of patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer.	Functional Assessment of Cancer Therapy-Ovarian (FACT-O), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, and ORZORA QoL Additional Items Questionnaire.
To describe patterns of routine clinical use of olaparib, the nature and patterns of adverse events (AEs) of nausea and vomiting and their impact on QoL in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer. To describe nausea/vomiting toxicity management patterns used in routine clinical practice.	Safety summary tables, Functional Living Index-Emesis (FLIE) Questionnaire, and concomitant medication use.

2.3 Safety objectives

Safety Objective:	**Outcome Measure:**
To assess the safety and tolerability of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer.	AEs/serious adverse events (SAEs)/AEs of special interest (AESI)

2.4 Exploratory objectives

Exploratory Objectives:	**Outcome Measure:**
To describe the longer term safety of olaparib monotherapy, including follow up for Myelodysplastic Syndrome (MDS)/ Acute Myeloid Leukaemia (AML)/ New primary malignancies.	Collection of long term adverse events, including MDS/AML or new primary malignancies
To correlate the incidence of side effects and QoL according to age and the presence of comorbidities.	Based on collected and summarised outcomes and comorbidities
To describe the clinical effectiveness of (response to) subsequent line of treatment and correlating it with the progression-free interval (PFI) (artificial prolongation of PFI through olaparib).	Description of maximum response to subsequent line of treatment
To describe the efficacy of olaparib according to the previous therapy, with or without bevacizumab, and according to the PFI (recurrence during or after the end of bevacizumab maintenance).	Based on collected and summarised outcomes
To describe the activity of olaparib according to the germline mutational status (*BRCA1* vs *BRCA2*), and to the presence of family history (yes vs not).	Based on collected and summarised outcomes and family history
To describe the kinetic of CA-125 progression according to Gynecological Cancer InterGroup (GCIG) criteria and its correlation with disease progression by RECIST 1.1 guidelines during olaparib therapy.	Based on collected and summarised outcomes

Exploratory Objectives:	**Outcome Measure:**
To measure loss of heterozygosity (LOH) for the *BRCA1* and *BRCA*2 genes in tumour samples and explore any potential association with efficacy.	Based on all available tumour samples collected and summarised outcomes.
To describe the real world clinical effectiveness and safety of olaparib maintenance monotherapy in patients with *BRCA*-independent HRRm ovarian cancer, by the following: • Investigator assessed PFS according to RECIST 1.1 • OS • Safety and tolerability.	a) Time from study enrolment to disease progression (assessed according to RECIST 1.1 guidelines) or death b) Time to death c) AEs, SAEs, AESI
Potential exploratory research into frequency, nature and predictive value of HRR gene mutations, including *BRCA1* and *BRCA2*, may be performed on the optional collected and stored tumour samples available at study entry or tumour biopsy samples collected during the course of the study. These could include studying resistance mechanisms to olaparib, future exploratory research into factors that may influence development of cancer and/or response to study treatment. To collect and store deoxyribonucleic acid (DNA) (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response to study treatment and or susceptibility to disease (optional)*.	
To explore the feasibility of reliably measuring s*BRCA*m and HRRm from circulating tumour DNA (ctDNA)*	

* These exploratory analyses may not be reported in the clinical study report (CSR), if not they will be reported separately.

3. PATIENT SELECTION, ENROLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion and none of the exclusion criteria for this study. These are designed in line with the EU approved indication for patients carrying *BRCA* mutated ovarian cancer. Under no circumstances can there be exceptions to this rule.

Patients with unknown germline *BRCA* mutation status, or patients found to carry g*BRCA*wt disease, or patients previously identified as having *BRCA*m disease based on a tumour test (with unknown g*BRCA* mutation status or with previously identified g*BRCA*wt status) will be considered for screening.

Patients previously diagnosed with g*BRCA*m disease will not be included in this study.

Patients with unknown *BRCA* mutation status who are considered for inclusion in this trial should be identified early so that the appropriate *BRCA* mutation screening procedures can be put in place in a timely manner.

In order to optimise the screening of patients and potential timely treatment initiation with study drug, patients may start the screening procedure from the end of cycle 3 of their current chemotherapy, if they are responding to treatment in the opinion of the investigator.

BRCA mutation status will be determined or confirmed through central blood and tumour testing as outlined in Figure 2 (see also Section 5.7.6).

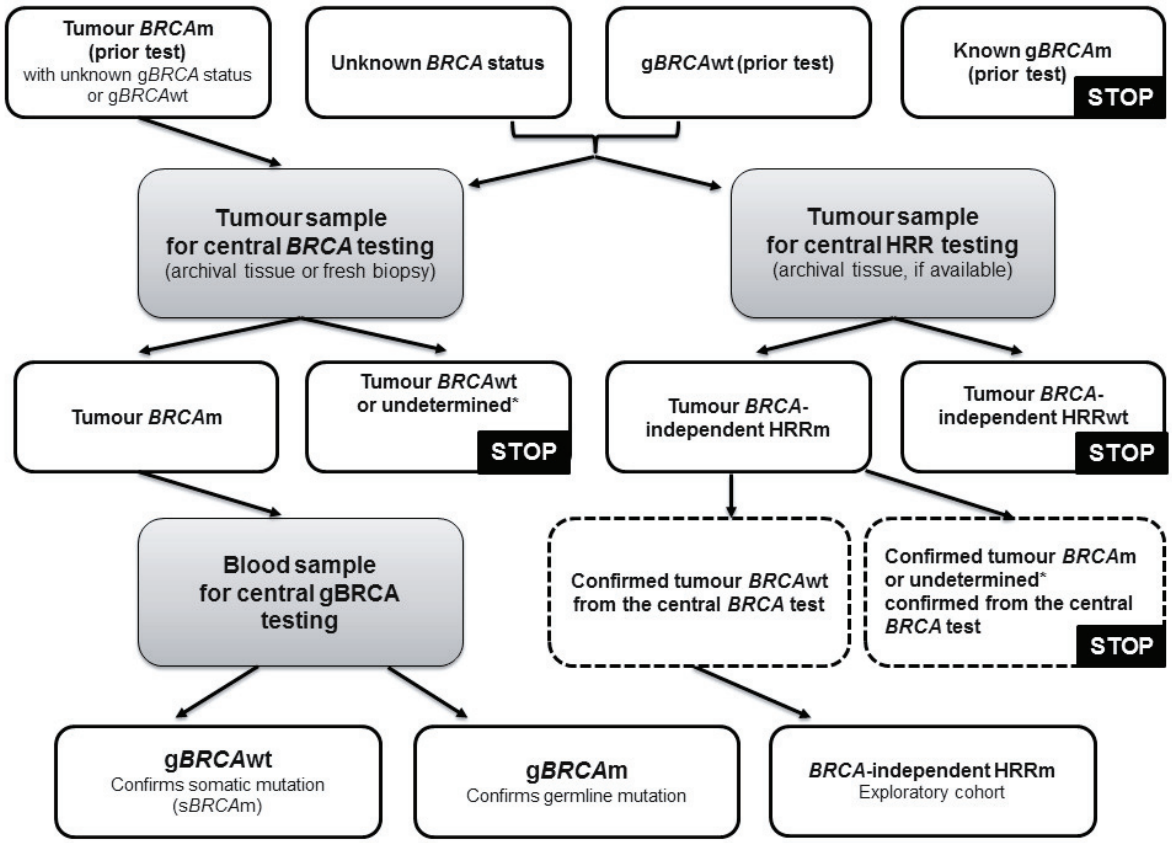
Exploratory HRRm patient cohort

Patients screened for the study with unknown *BRCA* status or with known g*BRCA*wt status, for whom an adequate archival tumour tissue sample is available, will be tested for qualifying HRR gene alterations, as defined in Section 1.1.4.

Patients found not to carry a *BRCA* mutation in their tumour (tumour *BRCA*wt), and with qualifying *BRCA*-independent HRR genetic alterations will be included in the study (HRRm cohort), and analysed as a separate exploratory cohort.

Patients previously identified as having *BRCA*m based on a tumour test will not be screened for HRR gene mutations.

Figure 2 Screening Flow Chart



*Undetermined: the central tumour BRCA testing was unable to determine the presence or absence of BRCA mutation.

3.1 Inclusion criteria

Screening procedures described in Section 3 should be strictly complied with. For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures
2. Age 18 years or over
3. Documented germline or somatic mutation in *BRCA1* or *BRCA2* genes that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) [Genetic counselling for patients with germline BRCA mutations should be performed according to local regulations]

   Or

Tumour *BRCA*wt status and documented qualifying mutation in any of 13 genes involved in the HRR pathway, excluding *BRCA1* and *BRCA2* (*ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*), identified by the Lynparza HRR Assay in archival tumour tissue (i.e., *BRCA*-independent HRRm)

4. Patients with platinum sensitive relapsed high grade epithelial ovarian cancers (including primary peritoneal and/or fallopian tube cancer):

   – Platinum sensitive disease is defined as disease progression ≥6 months after completion of their last dose of platinum based chemotherapy

5. Patients should have received at least 2 previous lines of platinum containing therapy prior to enrolment:

   – For the last chemotherapy course immediately prior to enrolment on the study, patients must be, in the opinion of the investigator, in response (partial or complete radiological response) and no evidence of a rising CA-125, following completion of this chemotherapy course.

6. Patients must have normal organ and bone marrow function measured within 28 days of enrolment, as defined below:

   – Haemoglobin ≥ 10.0 g/dL with no blood transfusions in the past 28 days

   – Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

   – Platelet count ≥ 100 x 10^9/L

7. Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN), Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase [SGOT]) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase [SGPT]) ≤ 2.5 x institutional ULN unless liver metastases are present in which case they must be ≤ 5x ULN

8. Creatinine clearance > 50 ml/min (calculated)

9. Patients must be postmenopausal or have evidence of non-childbearing status for women of childbearing potential.

   Postmenopausal is defined as any of the following:
   - Amenorrhoea for 1 year or more following cessation of exogenous hormonal treatments
   - For women under 50 years old, luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range
   - Radiation-induced oophorectomy, with interval of 1 year or more since last menses

- Chemotherapy-induced menopause, with interval of 1 year or more since last menses
- Surgical sterilisation (bilateral oophorectomy or hysterectomy).

3.2 Exclusion criteria

Screening procedures described in Section 3 should be strictly complied with and patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Patients previously diagnosed with g*BRCA*m disease
2. Participation in another clinical study with an investigational product during the most recent chemotherapy course
3. Patients with a known hypersensitivity to olaparib or any of the excipients of the product
4. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) or major surgery within 3 weeks prior to olaparib treatment. Major surgery within 3 weeks of starting study treatment and patients must have recovered from any effects of any major surgery
5. Persistent toxicities Common Terminology Criteria for Adverse Event (CTCAE) grade 2 caused by previous cancer therapy, excluding alopecia
6. Patients with myelodysplastic syndrome/acute myeloid leukaemia
7. Immuno-compromised patients e.g., Human Immunodeficiency Virus (HIV) requiring treatment or active Hepatitis B or C
8. Patients with symptomatic uncontrolled brain metastases. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease (SD) for 28 days
9. Patients considered to be at a high medical risk due to a serious, uncontrolled medical disorder, systemic disease or active, uncontrolled infection
10. Currently pregnant (confirmed with a positive pregnancy test) or breastfeeding.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment

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

The Investigator(s) will:

- Obtain signed informed consent from the potential patient before any study specific procedures are performed.
- Assign potential patient a unique enrolment number, beginning with 'E#'. This number is obtained through Interactive Voice/Web response System (IVRS/IWRS).
- Determine patient eligibility. See Section 3.
- If patient meets eligibility criteria enrol patient through IVRS/IWRS to dispense the IP.

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

3.4 Procedures for handling incorrectly enrolled patients

Where a patient does not meet all the eligibility criteria but is incorrectly enrolled and started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Not applicable.

3.6 Methods for ensuring blinding

Not applicable.

3.7 Methods for unblinding

Not applicable.

3.8 Restrictions

Patients of childbearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception in combination throughout the period of taking treatment and for at least one month after last dose of study drug.

For details refer to Appendix E.

3.9 Discontinuation of investigational product

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

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)
- Severe non-compliance with the study protocol
- Disease progression (unless in the investigator's opinion the patient is benefiting from the treatment and does not meet any other discontinuation criteria)

3.9.1 Procedures for discontinuation of a patient from investigational product

By discontinuing from IP, the patient is not withdrawn from the study unless the patient withdraws consent to participation in the study. If a patient is withdrawn from study, see Section 3.10.

At any time, patients are free to discontinue investigational product or withdraw from the study, without prejudice to further treatment. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any adverse events. Any patient discontinuing IP should be seen at 30 days post last dose of IP for the evaluations outlined in the study schedule. After discontinuation of IP, the Principal Investigator (PI)/Sub-Investigator will perform the observation(s), test(s) and evaluation(s) consistent with the current standard of care as well as give appropriate medication and all possible measures for the safety of the patient. Patients who discontinue treatment prior to documented progression should continue to be followed for first progression as per the protocol recommended schedule. Once progressed, all patients should be followed for PFS2 and OS as per the protocol schedule. In addition, they will record on the electronic case report form (eCRF) the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation. If patients discontinue olaparib, the study monitor must be informed immediately. Patients will be required to attend the treatment discontinuation visit. The patient should return all IP.

After discontinuation of olaparib 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 patients underlying disease, or the patient is lost to follow up (see Section 4.3.1). All new AEs and SAEs occurring during the 30 calendar days after the last dose of olaparib must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 6.5) and followed to resolution as above. Patients should be seen at least 30 days after discontinuing the last IP dose to collect and / or complete AE information. Any untoward adverse event occurring subsequent to that the investigator assesses as possibly related to the study medication should also be reported as an adverse event. Cases of MDS, AML or new primary cancers, as well as pneumonitis should be reported also after the 30-day follow-up AE reporting period.

Any patient who has not yet shown disease progression at withdrawal from IP should continue to be followed as detailed in Table 3.

All patients should be followed for survival, up to the final analysis.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be enrolled. These patients should have the reason for study withdrawal recorded as 'Did not meet Eligibility Criteria' (i.e., patient does not meet the required inclusion/exclusion criteria), and screening failure/ study withdrawal should be noted in IVRS/IWRS. This reason for study withdrawal is only valid for screen failures (not enrolled patients). Patients who were screen failures may be re-enrolled and re-screened if in the opinion of the Investigator, the reason(s) for earlier withdrawal no longer applies. Patients cannot re-enter the study if dosed and subsequently withdrawn from the study.

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then her unique enrolment number cannot be reused. Withdrawn patients will not be replaced.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Schedule Screening

	Part 1 *BRCA* testing	**Part 2** Patients with known tumour *BRCA* mutation
	Post-cycle 3 of ongoing chemotherapy to -28 days[a]	**-28 to –1 days**
Informed consent	X[b]	X[i]
Demographics		X
Medical and surgical history		X
Inclusion/exclusion criteria		X
ECOG Performance Status (0-2)		X
Vital signs, body weight, (includes blood pressure [BP] and pulse)		X
Haematology / clinical chemistry[c]		X
Pregnancy test		X
Tumour Assessment (CT or MRI according to RECIST 1.1 guidelines)[d]		X
Blood sample for disease specific marker (CA-125)		X
Tumour sample for determination of tumour *BRCA* status	X[e]	X[e]
Blood sample for determination of g*BRCA* status	X[f]	X[f]
Tumour sample for HRR testing	X[g]	
Adverse Events (from time of consent)	X[h]	X[h]
Relevant concomitant medications		X
Optional tumour sample for exploratory analysis		X[j]

a The post cycle 3 of ongoing chemotherapy to -28 day time period is to allow patients with unknown *BRCA* mutation status who are considered for inclusion in this trial to be identified early so that the appropriate *BRCA* mutation screening procedures can be put in place in a timely manner. In order to optimize the screening of patients and potential timely treatment initiation with study drug patients may start the screening procedure from the end of cycle 3 of their current chemotherapy if they are, in the opinion of the investigator, in partial or complete response.

b Informed consent for *BRCA* testing and HRR testing only.

c Coagulation tests will only be required if clinically indicated.

d Computed Tomography (CT)/ Magnetic Resonance Imaging (MRI) of the chest, abdomen and pelvis not more than 28 days prior to starting olaparib and as close as possible to the start of olaparib.

e As part of the study screening procedures, an archival tumour sample should be provided for central determination or confirmation of *BRCA*m status. If an archival tumour sample is not available, a fresh biopsy should be provided (see Sections 5.7.1 and 5.7.6 for further details).
- For patients with unknown *BRCA*m status and patients with previously identified g*BRCA*wt status, tumour *BRCA*m status will be determined by central laboratory testing on tumour samples.
- Patients who have been previously identified as having *BRCA* mutations in the tumour, determined in a local test, can enter screening Part 2; however confirmatory central test from tumour should be completed prior to enrolment.

f Blood samples for central determination of g*BRCA* status will be collected from patients who are found to carry a tumour BRCA mutation based on the central tumour test (see Sections 5.7.4 and 5.7.7).
- This result will be used to confirm patients' germline or somatic *BRCA* mutated disease, and the test should be completed prior to study enrolment.
- Patients who have been previously identified as having *BRCA* mutations in the tumour and enter the study at Part 2 screening as either known somatic patients based on the local testing, or tumour *BRCA* with unknown germline status, can be enrolled into the study after central confirmation of their *BRCA* tumour mutation status and blood sample collection for central confirmation of the germline or somatic *BRCA* mutation status.

g As part of the study screening procedures, if available, an archival tumour sample should be provided for central determination of *BRCA*-independent HRR mutation status. If an adequate archival tumour sample is not available for this test, it will not be conducted (see Section 5.7.2 for further details).

h Only SAE's related to screening procedures will be collected at this visit.

i Informed consent for participation in the main study, including optional consent for tumour and blood samples for exploratory analysis.

j All patients are requested to provide samples of their most recently available tumour tissue for exploratory testing (optional and subject to specific informed consent). This is to be provided in addition to the diagnostic samples for tumour *BRCA* and HRR testing (see Section 5.7.3).

Table 2 Study Schedule – On Study Treatment and Discontinuation

Visit Number	**2**	**3**	**Visit No. 4 onwards** Subsequent on treatment visits every 4 weeks[a] Tumour assessment visits every 12 weeks[a,b]	**Discontinuation of olaparib**	**Safety Follow-up 30 days after last dose of IP**
Day	1	29	Day 1of next visit period (Visit 4 equals day 57 (week 8) then visit 5 equals day 85 (week 12) etc.)		
Visit Window		*±3d*	*±3d*	*±7d*	*±7d*
Enrolment	X				
Haematology / clinical chemistry[c]	X[c]	X[c]	X	X	X
Blood sample for disease specific marker (CA-125)	X[i]	X[i]	X[i]	X[i]	
Blood samples for ctDNA analysis		X[j]			
Tumour Assessment (CT or MRI according to RECIST 1.1 guidelines)[b]			Every 12 weeks until PD		
FACT-O[g]	X	X	X	X	X
FACIT-Fatigue[g]	X	X	X	X	X
ORZORA QoL Additional Items Questionnaire [g]	X	X	X	X	X
Adverse Events[d]	X	X	X	X	X
FLIE[g, h]	X[h]	X[h]	X	X	X
Concomitant medications including blood transfusions	X	X	X	X	X

Table 2 Study Schedule – On Study Treatment and Discontinuation

Visit Number	**2**	**3**	**Visit No. 4 onwards** Subsequent on treatment visits every 4 weeks[a] Tumour assessment visits every 12 weeks[a,b]	**Discontinuation of olaparib**	**Safety Follow-up 30 days after last dose of IP**
Day	1	29	Day 1of next visit period (Visit 4 equals day 57 (week 8) then visit 5 equals day 85 (week 12) etc.)		
Visit Window		*±3d*	*±3d*	*±7d*	*±7d*
Olaparib dispensed/returned[e]	X	X	X	X	
Subsequent cancer therapy following discontinuation of olaparib[f]					X
Optional tumour sample on progression[j]				X	

a Visit to take place on Day 1 of a 4 week (28 day) visit period up to 52 weeks (if not progressed and still on treatment) as per IB or prescribing information as applicable based on country specific marketing authorisation status, then on day 1 of a 12 week visit period relative to date of enrolment. Visits for patients who remain on treatment post progression should take place every 12 weeks.

b Follow-up tumour assessment visits will be performed every 12 weeks (±1 week) relative to date of enrolment. Follow-up CT or MRI assessments will cover chest (in those patients with disease in the chest or upper abdomen lymphadenopathy at baseline), abdomen and pelvis. Any other sites at which new disease is suspected should also be appropriately imaged. Patients will be followed until disease progression according to RECIST 1.1 guidelines. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

c Safety blood samples do not need to be repeated on Day 1 of olaparib treatment if assessed within 7 days before starting olaparib, unless the investigator believes that it is likely to have changed significantly. Coagulation tests only required if clinically indicated. For a list of all required laboratory tests please refer to Section 5.2.1

d When an AE for nausea and vomiting occurs, an additional eCRF will require completion. All ongoing adverse events/serious adverse events (AEs/SAEs) and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution as per Section 6.4.3.

e Sufficient olaparib 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.

f Post discontinuation of olaparib all anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the investigator's opinion of response to them plus the date of progression need to be recorded.

g QoL questionnaires will be collected at baseline, at Day 29, then every 12 weeks (+/- 7 days) for 24 months or the data cut off for the primary analysis, whichever comes first. In addition, QoL questionnaires will be collected at the discontinuation of study treatment visit and 30 days post last dose.

h In addition to the outlined QoL collection frequency, in the first month from starting the study treatment, the FLIE questionnaire will be administered to the patient weekly, in person or over the phone.

i Assessment of CA-125 will be at the discretion of the investigator, according to the local clinical practice.

j To be collected only for patients that have confirmed s*BRCA*m or HRRm ovarian cancer (optional and subject to specific informed consent). If confirmation of the s*BRCA*m status is not obtained by Day 29, these blood samples can be taken at a later study visit.

h Optional and subject to specific informed consent.

Table 3 Study Schedule – Follow-up Post Discontinuation of Olaparib

Visit Number	Off treatment follow-up Olaparib discontinued due to reasons other than disease progression	Follow-up for patients beyond 1st disease progression (PFS1)
	Follow up for 1st progression Tumour assessment visits every 12 weeks[a]	Every 12 weeks post discontinuation of olaparib
Visit Window	±7d	±7d
Tumour Assessment (CT or MRI according to RECIST 1.1 guidelines) [a]	Every 12 weeks until PD, one additional RECIST 1.1 assessment required after PD declared by the investigator	
Blood sample for disease specific marker (CA-125)	X[g]	
FACT-O[f]	X	X
FACIT-Fatigue[f]	X	X
ORZORA QoL Additional Items Questionnaire [f]	X	X
Adverse Events[e]	X[e]	X[e]
FLIE[f]	X	X
Subsequent cancer therapy following discontinuation of olaparib[b]	X	X
Time to second progression		X
Survival[c,d]	X	X

a RECIST 1.1 follow-up assessments will be performed as per the original schedule every 12 weeks (±1 week) relative to date of enrolment. Follow-up assessment will include CT or MRI assessments of abdomen and pelvis for all patients. Follow-up chest CT will be performed in patients with thoracic lesions or upper abdomen lymphadenopathy identified at baseline assessment. Any other sites at which new disease is suspected should also be

appropriately imaged. Patients will be followed until disease progression as per RECIST 1.1 guidelines. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

b All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the investigators opinion of response to them, significant patient toxicity arising from their use plus the date of progression, post discontinuation of olaparib need to be recorded

c The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

d In addition to their regular 12 weekly contact, patients will be contacted in the 7 days following a specified date (data cut-off date) for each survival analysis.

e See section 6.4.3 for reporting of adverse events after the 30 day follow up period.

f QoL questionnaires will be collected every 12 weeks (+/- 7 days) for 24 months or the data cut off for the primary analysis, whichever comes first. Patients who had disease progression will complete the questionnaires during the 12 weekly survival follow ups either in person or over the phone.

g Assessment of CA-125 will be at the discretion of the investigator, according to the local clinical practice.

4.1 Enrolment/screening period

Procedures will be performed according to the Study Plan in Table 1. Each potential patient will provide written informed consent prior to any study specific procedures and undergo assessments applicable for the visit.

Patients with unknown germline *BRCA* mutation status, or patients found to carry g*BRCA*wt disease, or patients previously identified as having *BRCA*m disease based on a tumour test (with unknown g*BRCA* mutation status or with previously identified g*BRCA*wt status) will be considered for screening.

Patients previously diagnosed with g*BRCA*m disease will not be included in this study. Patients with unknown *BRCA* mutation status who are considered for inclusion in this study may start the screening procedure from the end of cycle 3 of their current chemotherapy, if they are responding to treatment in the opinion of the investigator.

All patients who wish to participate in the study will have to consent to undergo tumour and germline *BRCA* testing as required as part of the screening procedures, depending on the sequence of testing and results from each test. *BRCA* mutation status will be determined or confirmed through central blood and tumour testing as outlined in Figure 2 (see also Section 5.7.6). Tumour *BRCA* mutation status will be determined by central laboratory test on tumour samples. An archival tumour sample should be provided for central determination of *BRCA* status. If an archival tumour sample is not available, a fresh biopsy should be provided (see section 5.7.1 for further details). Blood samples for central determination of g*BRCA* status will be collected from all patients who are found to carry a tumour *BRCA* mutation based on the central tumour test. This result will be used to confirm patients' germline or somatic *BRCA* mutated disease (the latter with mutation present only in the tumour), and the test should be completed prior to study enrolment.

Patients with unknown *BRCA* status and patients with prior assessment of g*BRCA*wt status will be screened for tumour *BRCA* mutation as described above and will start the study from screening Part 1 and continue to Part 2, if applicable. Patients who have been previously identified as having *BRCA* mutations in the tumour, determined in a local test (with unknown germline status or previously confirmed g*BRCA*wt status) can start the study from screening Part 2. However, confirmatory central test from tumour sample should be completed prior to enrolment. They can be enrolled in the study after central confirmation of the tumour *BRCA* mutation, and blood sample collection for central confirmation of the germline or somatic *BRCA* mutated disease.

All patients will be asked to consent to and provide an adequate archival tumour sample, if available, for tissue-based HRR gene panel mutation testing using the investigational Lynparza HRR Assay from CCI Patients previously identified as carrying *BRCA*m ovarian cancer based on a tumour test will not be asked to consent to and provide a tumour sample for HRR testing. HRR tumour testing will be performed in parallel to the central *BRCA* tumour testing. Patients with *BRCA*wt tumour status who carry one or more *BRCA*-independent

qualifying HRR gene alterations (as defined in Section 1.1.4) will be assigned to the exploratory HRRm study cohort (see Section 5.7.2).

Additionally, all patients will be also asked to provide consent to supply optional tumour samples for exploratory analysis, and optional blood samples (collected only for patients with s*BRCA*m or HRRm disease). This consent is included in the main patient informed consent form. However, consent for providing these samples is optional and will not prevent patients from enrolment into the study.

4.2 Treatment period

Descriptions of the procedures for this period are included in the Study Plan, Table 2 and Table 3.

4.3 Follow-up period

Patients should be discontinued from olaparib if any discontinuation criteria are fulfilled (see Section 3.9). The assessments to be carried out at the visit are detailed in the study schedule (Table 2 and Table 3).

4.3.1 Follow-up 30 days after last dose of investigational product (IP)

A follow-up visit should be conducted 30 days after the last dose of olaparib. Any serious and/or non-serious AEs ongoing at the time of the Discontinuation Visit or which have occurred during the defined 30-day follow-up period must be followed-up. Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the eCRF. The assessments to be carried out at the 30-day follow up visit are detailed in the study schedule (Table 2 and Table 3).

4.3.2 Survival

Assessments for survival should be made every 12 weeks following disease progression. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. Survival data will be collected up to the time of the final overall survival (OS) analysis. In addition, patients should be contacted in the week following the data cut-off for the primary PFS and final survival analyses to provide complete survival data.

Patients will be followed up as per Table 3 to the point of the final analysis. At this point investigators will be notified that no further data collection for the study is required. Monitoring and recording of SAEs will continue as per Section 6.4.3.

The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients general practitioner and checking

publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

4.3.3 Second progression (PFS2)

Patients should be assessed every 12 weeks for a second progression (using the patient's status at first progression as the reference for assessment of second progression). A patient's progression status is defined according to local standard clinical practice and may involve any of objective radiological, CA-125, clinical progression or death. The date of PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

4.3.4 Patient management post primary analysis

The data cut-off for the statistical analysis for the primary objective in the patients enrolled with *BRCA*m will be at 60% maturity for PFS analysis.

Patients on olaparib at the time of the data cut-off will continue to receive olaparib until they meet any discontinuation criteria as per Section 3.9.

Patients on olaparib will be followed for routine safety assessments as per protocol and as per EU olaparib Prescribing Information or per IB as appropriate depending on country specific marketing authorisation status. These patients should be followed for disease progression according to routine clinical practice but visits are recommended to take place at least every 12 weeks.

All patients (patients still on olaparib and patients withdrawn from olaparib) will be followed for survival and disease progression.

4.3.5 Patient management post final analysis

The data cut-off for the final statistical analysis of the study will be at approximately 60% OS maturity or a time point defined based on event rate and study closing timelines, whichever occurs first.

At this time point, the clinical study database will close to new data. Patients who are receiving olaparib can either choose to discontinue from the study or where the investigator believes patients are gaining clinical benefit, patients may continue to receive olaparib. All patients will receive follow-up care in accordance with standard local clinical practice.

AstraZeneca will continue to supply olaparib to patients after completion of this study if patients are considered to continue to benefit of olaparib treatment and no other discontinuation criteria are met.

SAEs will continue to be reported to AstraZeneca Patient Safety Department, for any patients who continue on olaparib until 30 days after olaparib is discontinued, in accordance with

Section 6.4.3. Additionally as stated, any SAE or non-serious adverse event that is ongoing at 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. If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AstraZeneca, Patient Safety. Investigators should also report MDS, AML or new primary cancer cases, as well as pneumonitis.

Drug accountability should continue to be performed until the patient stops olaparib completely.

5. STUDY ASSESSMENTS

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

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

5.1 Efficacy assessments

5.1.1 CT and MRI scans tumour assessments

It is required that all patients will have clinical and objective radiological tumour assessments performed according to RECIST 1.1 guidelines at baseline and every 12 weeks relative to date of enrolment, until objective radiological disease progression as determined by the investigator. All treatment decisions will be based on investigator's assessment of the scans according to RECIST 1.1 guidelines. It is expected that a minimum of 50 patients with s*BRCA*m disease will have efficacy assessments performed according to RECIST guidelines.

All patients should have assessments until documented evidence of objective radiological progression according to RECIST 1.1 guidelines, irrespective of treatment decisions (i.e., radiological follow up until progression even if a patient discontinues olaparib prior to progression and/or receives a subsequent therapy prior to progression). CT examination with intravenous (i.v.) contrast media administration is the preferred imaging modality. MRI should only be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method. In addition, FDG-PET, bone scintigraphy and ultrasound may also be used for identifications of new lesions only.

At baseline, the imaging modalities used for assessment should be performed by contrast enhanced CT (MRI where CT is contraindicated) scans of the chest, abdomen and pelvis with other regions as clinically indicated for the assessment of disease. Follow-up CT or MRI

assessments will cover chest (in those patients with disease in the chest or upper abdomen lymphadenopathy at baseline), abdomen and pelvis with any other regions imaged at baseline where disease was present. Any other sites at which new disease is suspected should also be appropriately imaged.

Sites should use the same modality and acquisition parameters to assess a patient at baseline and at subsequent follow-up, in order to ensure longitudinal consistency.

Radiological examinations performed in the conduct of this study should be retained at site as source data.

There will be no central review of CT and MRI scans in this study. Radiological reading will be performed at the site level only. All treatment decisions will be based on site assessment of scans.

5.1.2 **Tumour Evaluation**

RECIST 1.1 guidelines are mandated to be used to assess patient response to treatment by determining progression free survival (PFS) times, objective response rates (ORR) and duration of response (DoR). The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are presented in Appendix F.

CA-125 should not be directly used for assessing objective response or progression and patients should be continued on treatment until objective radiological disease progression.

Categorisation of objective tumour response assessment should be guided by RECIST 1.1 guidelines: complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), and not evaluable (NE). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of a response of progression, tumour response (CR, PR, SD or NE) will be calculated in comparison to the baseline tumour measurements obtained before enrolment.

For patients with non-measurable disease only at baseline, categorisation of objective tumour response assessment should be based on the RECIST 1.1 guidelines: CR, PD, Non CR/Non PD or NE (not evaluable).

If the investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesion (NTL) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit

discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Additionally, if in the investigator's opinion, the patient would continue to derive benefit from treatment with study drug beyond progression and no other discontinuation criteria are met, treatment with olaparib could be continued to a point as judged clinically by the treating physician.

Following progression, patients should continue to be followed up for survival every 12 weeks as outlined in the study plan (Table 2 and Table 3). It is important to follow the assessment schedules as closely as possible.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood samples for determination of clinical chemistry and haematology will be taken at the times indicated in the Study Plan.

Any clinical chemistry, haematology and urinalysis required as per prescribing information, where applicable, should be performed at a local laboratory at or near to the investigational site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variable listed in Table 4 will be measured.

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

Table 4 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
Mean Cell Volume (MCV)	S/P-Alkaline Phosphatase (ALP)
B- Neutrophil count (absolute count)	S/P-Aspartate Transaminase (AST)
B-Platelet count	S/P-Alanine Transaminase (ALT)
	S/P urea or Blood Urea Nitrogen (BUN)

5.2.1.1 Disease specific tumour marker samples (CA-125)

It is important to follow the assessment schedule as closely as possible. If CA-125 assessment is performed, patients should be evaluated based on progressive serial elevation of serum CA-125 according to the GCIG criteria (Rustin et al 2011) at the discretion of the investigator according to local clinical practice.

5.2.2 Vital signs

Vital signs will be performed at screening Part 2 and as clinically indicated thereafter.

Height will be assessed at screening only. Weight will be assessed at screening and as clinically indicated at any other time.

Any changes in vital signs should be recorded as an AE, if applicable.

5.2.2.1 Pulse and blood pressure

Blood pressure and pulse will be measured at baseline and as clinically indicated afterwards.

The date of collection and measurement will be recorded on the appropriate eCRF.

5.3 Other assessments

5.3.1 Patient reported outcomes

Patient Reported Outcomes (PROs), an umbrella term referring to all outcomes and symptoms, are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered in this study: Functional Assessment of Cancer Therapy-Ovarian (FACT-O), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, the ORZORA QoL Additional Items Questionnaire (a set of newly developed ovarian cancer items) and Functional Living Index-Emesis (FLIE). Each is described below.

5.3.2 Administration of PRO questionnaires FACT-O and FACIT-Fatigue

Paper questionnaires will be given to the patient at baseline, at Day 29, then every 12 weeks (+/- 7 days) for 24 months or the data cut off for the primary analysis, whichever comes first. In addition, QoL questionnaires will be collected at the discontinuation of study treatment visit and 30 days post last dose. Patients who had disease progression will complete the questionnaires during the 12 weekly survival follow ups either in person or over the phone (Table 3). Following collection of the paper questionnaire (in person or over the phone), the site staff should enter the information directly into the WBDC electronic database system.

Each centre must allocate the responsibility for the administration of the questionnaires to a specific individual (e.g., a research nurse, study coordinator) and if possible assign a back-up person to cover if that individual is absent. The AstraZenaca Study Delivery Team (or delegate) will provide relevant training in administration of the questionnaires. The significance and relevance of the data need to be explained carefully to participating patients so that they are motivated to comply with data collection.

The instructions for completion of the PRO questionnaires are as follows:

- Questionnaires must be completed prior to any other study procedures (following informed consent) and before discussion of disease progress to avoid biasing the patient's responses to the questions;

- Questionnaires must be completed in private by the patient, where a visit to the clinic is not planned, i.e., for patients followed up for survival with no scheduled clinic visits, the site staff will administer questionnaires via telephone;

- The patient should be given sufficient time to complete at their own speed;

- The patient should not receive help from relatives, friends or clinic staff to answer the questionnaire. However, if the patient is unable to read the questionnaires (e.g., is blind or illiterate) the questionnaires may be read out loud by trained clinic staff and the patient's verbal responses recorded;

- On completion of the questionnaire it should be handed back to the person responsible for questionnaires who should check for completeness;

- Only one answer should be recorded for each question.

5.3.3 Functional Assessment of Cancer Therapy-Ovarian (FACT-O)

Patient-reported health-related quality of life (HRQoL) will be assessed using the FACT-O questionnaire (Appendix H). The FACT-O is composed of the following sub-scales: physical, social/family, emotional, and functional well-being as well as the additional concerns scales consisting of specific ovarian cancer symptoms. The main end point for health-related quality of life analysis will be the Trial Outcome Index (TOI), an established single targeted index derived from the FACT-O questionnaire and it is considered to target the most relevant symptoms together with function and physical well-being and can be directly related to signs and symptoms and AEs. The TOI is composed of the following scales of the FACT-O: physical and functional well-being and additional concerns.

5.3.4 Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)

Subjects in the study will complete the FACIT-Fatigue (Appendix H). The FACIT-Fatigue is a 13-item subject-completed questionnaire to assess subjects' fatigue experience and its impact on their daily lives over the past 7 days. Sample items include "I feel fatigued," "I feel weak all over," and "I feel listless (washed out)." Responses range from 0 (= not at all) to 4 (= very much). By scoring convention, after appropriate reverse scoring of 11 items, lower scores on the FACIT-Fatigue subscale indicate greater levels of fatigue. Final scores are the sum of the responses (0-52) where higher scores indicate better HRQoL (Yellen et al 1997). Changes in scores ≥ 3 points are considered to be clinically meaningful (Cella et al 2002).

5.3.5 ORZORA QoL Additional Items Questionnaire

In addition to FACT-O and FACIT-Fatigue, subjects will also complete the following set of newly developed ovarian cancer items: "I feel ill with low energy," "I am able to enjoy life and I am still interested in my hobbies and interests," "I am satisfied that my family understands my disease," "I feel I am able to meet the needs of my family," "I understand the need to take my medication and my treatment regimen," "My treatment has had significantly negative effects on my QoL," and "I feel like a normal woman" with the same recall period (7

days) and response options as in FACT-O. Finally, on a free text response scale, subjects will be asked to respond to the following question: "What are the 3 most significant issues you are struggling with, please list them starting with your worst first?"

5.3.6 Functional Living Index-Emesis (FLIE)

The Functional Living Index-Emesis (FLIE) tool (Lindley et al 1992) will be used to assess study treatment-induced nausea and vomiting and will be assessed at the time points detailed in Table 2 and Table 3 of the study schedule. Further details will be provided in the SAP.

5.4 Pharmacokinetics

5.4.1 Collection of samples

Pharmacokinetic (PK) samples will not be taken during the study.

5.4.2 Determination of drug concentration

Not applicable.

5.4.3 Storage and destruction of pharmacokinetic samples

Not applicable.

5.5 Pharmacodynamics

5.5.1 Collection of samples

Pharmacodynamic samples will not be taken during the study.

5.5.2 Storage, re-use and destruction of pharmacodynamic samples

Not applicable.

5.6 Pharmacogenetics

Pharmacogenetic samples will not be taken during the study.

5.6.1 Collection of pharmacogenetic samples

Not applicable.

5.6.2 Storage, re-use and destruction of pharmacogenetic samples

Not applicable.

5.7 Biomarker analysis

The patient's consent before the use of donated biological samples for any biomarker analyses is mandatory.

Biological samples (e.g., archived tumour samples) will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

5.7.1 Collection of tumour sample for *BRCA* testing at screening (mandatory)

All patients will be asked to provide a tumour sample for *BRCA* testing as part of the study screening procedures. The consent for this will be obtained prior to retrieving the archival tumour sample or obtaining the tumour tissue. In patients who have been previously identified as having *BRCA* mutations in the tumour, determined in a local test, collection of an archival tumour sample is performed to allow the central confirmation of the tumour *BRCA* mutation (see Section 5.7.6).

Further exploratory work to elucidate the mechanism of response, understand the mode of action of study treatment, or improve the understanding of disease progression may be performed on surplus tumour tissue. The consent for this exploratory analysis is optional and has been included in the main consent form.

Historical tumour tissue paraffin block from resection or a core biopsy from the primary tumour or metastases should be provided. The portion of tumour within the block should be 20% at a minimum. This sample will have been collected anytime since the time of original diagnosis but prior to study entry. Alternatively, sections mounted on glass slides prepared from the block can be provided.

Please refer to the Myriad Instructions For Use for further details of archival tissue collection, shipping and storage.

5.7.2 Collection of tumour sample for HRR testing

All patients with adequate archival tissue, with the exception of patients previously identified as carrying BRCAm ovarian cancer based on a tumour test, will be asked to provide a formalin fixed and paraffin embedded (FFPE) tumour sample for tissue-based HRR gene panel mutation testing using the investigational Lynparza HRR Assay from CCI

The exploratory cohort of HRRm patients will be defined by having *BRCA*wt tumour status by the test performed by Myriad, and one or more *BRCA*-independent qualifying LOF mutations in any of 13 HRR genes identified by the Lynparza HRR Assay on an archival tumour sample.

The Lynparza HRR Assay is an investigational NGS-based assay that will be performed as a single laboratory testing service using DNA extracted from the provided tissue sample.

The tumour sample will be tested for the following mutation in 15 biomarkers simultaneously: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D*, and *RAD54L*.

For each patient that passes tissue sample quality control, CCI will generate a report to investigators; results concerning *BRCA1* and *BRCA2* will not be reported. A patient is

classified "positive" if one or more qualifying genetic alterations are found in any of the 13 HRR genes (the 15 abovementioned excluding *BRCA1* and *BRCA2*). Patients that do not meet such criteria are labelled as biomarker "negative".

Patients who do not have an adequate tumour tissue sample for HRR testing will continue screening as described in Sections 5.7.1, 5.7.4, 5.7.6 and 5.7.7. They remain eligible for the study if they are found to carry a germline or somatic *BRCA* mutation by the test performed by Myriad.

Tumour samples for HRR testing must meet the following criteria:

- An unstained, archival FFPE tumour tissue sample of sufficient quantity and quality (as specified in the CCI Central Laboratory Services Manual) to allow for central analysis of HRR gene mutation. Archival tissue samples may be from primary or metastatic tumour deposits. Archival bone metastases are not accepted. Provision of blocks is encouraged wherever possible.

- If a tumour block is not available pre-cut 5 µm thick unstained sections from FFPE tissue block may be provided. The number of sections to be supplied are detailed in the CCI Central Laboratory Services Manual.

Any residual samples will be used for exploratory research by AstraZeneca, only in cases where optional consent has been provided. Residual tissue may be returned to site upon individual request.

5.7.3 Collection of tumour sample for exploratory analysis at screening and at disease progression (optional)

All patients enrolled will be asked at screening to provide consent for optional most recent archival tumour tissue sample for exploratory analysis. Date that this sample was taken from the patient should after that of the mandated archival sample used to determine or confirm the tumour *BRCA* mutation. The consent for this is optional and has been included in the main consent form. Additionally, wherever possible, and also subject to optional informed consent, an on-study tumour biopsy sample obtained either from the progressed lesion or from a new lesion may be collected at disease progression, in order to perform exploratory testing. Biopsies may be particularly valuable where there is a marked phenotypic change in a particular lesion.

Tumour tissue collected during the study should be immediately fixed and processed to a FFPE block. Alternatively, sections mounted on glass slides prepared from the block can be provided.

In both cases, material will be used for additional exploratory work, which may be conducted to elucidate the mechanism of response, understand the mode of action of study treatment, or improve the understanding of disease progression.

Please refer to the CCI Central Laboratory Services Manual for further details regarding tissue collection, shipping and storage.

5.7.4 Exploratory use of data generated from CCI Central testing of tumor sample (Optional)

The designated, investigational Lynparza HRR Assay involves the analysis of 13 HRR genes for the presence of qualifying mutations in this study. The gene panel used in this investigational test is based on the clinical-grade CCI test platform that generates results for 324 cancer-related genes. A full list of all 324 genes is available in the CCI Central Laboratory Services Manual. Patients will be asked to give optional consent to the use of this additional gene data by AstraZeneca for exploratory research, biomarker analysis in relation to olaparib, the study of ovarian cancer and development of future diagnostic tests.

5.7.5 Collection of blood sample for germline *BRCA1 and BRCA2* testing

For patients who are confirmed as having a tumour *BRCA*m status a 7 mL blood sample will be requested to test for germline *BRCA* mutations using the current commercial Myriad BRAC*Analysis*® test. Blood samples should not be collected and shipped until a tumour *BRCA* result has been received from Myriad.

Please refer to the Myriad Instructions For Use for further details of blood collection, shipping and storage.

5.7.6 Collection of blood sample for ctDNA analysis

For patients who have confirmed s*BRCA*m or HRRm disease, three 10 mL blood samples for collection of plasma will be taken on visit 3 (day 29) for the purpose of exploring the potential of determining s*BRCA*m and HRRm status via analysis of ctDNA. The consent for this is optional and has been included in the main consent form. If sBRCAm status is not known at Day 29, these samples can be taken at a later study visit.

Please refer to the CCI Central Laboratory Services Manual for further details regarding blood sample collection, shipping and storage.

5.7.7 Guidance for *BRCA* and HRR testing

Patients previously diagnosed with g*BRCA*m disease will not be included in this study.

Patients with unknown germline *BRCA* mutation status or patients found to carry g*BRCA*wt disease or patients previously identified as having *BRCA*m disease based on a tumour test (with unknown g*BRCA* mutation status or with previously identified g*BRCA*wt status) will be considered for screening.

All patients who wish to participate in the study will have to consent to undergo tumour and germline *BRCA* testing as required as part of the screening procedures

All patients considered for screening will provide an archival tumour sample to allow central tumour *BRCA*m testing.

For patients with unknown *BRCA* mutation status and patients with g*BRCA*wt disease (based on a previous blood test), tumour *BRCA* mutation status will be determined by central testing on the archival tumour sample.

For patients who have been previously identified as having *BRCA* mutations in the tumour, on the basis of a local tumour test, central testing will be used to confirm the tumour *BRCA* mutation status.

All patients found or confirmed to carry a deleterious or suspected deleterious *BRCA* mutation in the tumour based on the central tumour test are eligible to enter the study, providing that they meet the other eligibility criteria.

A blood sample for central determination of the germline *BRCA* status will be collected as part of the screening procedures from all patients who are found to carry a *BRCA* mutation in the tumour based on the central tumour test. Central germline testing will also be performed for patients previously identified as having g*BRCA*wt disease based on a local test.

The result of this blood test will be used to confirm the patient's germline or somatic *BRCA* mutated disease, the latter by the absence of the same specific *BRCA* mutation that has been found in the patient's tumour. Patients will need to have met the local ethical requirements for such genetic tests (e.g., genetic counselling) prior to the test procedure. Although all women with ovarian cancer would be supported to be tested as part of the screening for inclusion in the study, the following clinical and pathological features are known to play a role in association with an increased probability of *BRCA* mutations:

1. Family history of breast or ovarian cancer, ethnicity and age

2. High grade epithelial ovarian cancer.

Patients who have no *BRCA* mutation in the tumour may be eligible for the study if they carry one or more *BRCA*-independent qualifying mutations in any of 13 HRR genes identified by the Lynparza HRR Assay (HRRm exploratory cohort).

To enable the completion of the screening procedure within an 8-week window after the last dose of platinum-based therapy, HRR tumour testing will be performed in parallel to *BRCA* tumour testing, on two different tumour samples. Patients who have only one available tumour block will be tested only for *BRCA* mutated disease.

5.7.8 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.7.9 Labelling and shipment of biological 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 '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 and appropriate labelling, shipment and containment provisions are approved.

5.7.10 Chain of custody of biological samples

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

The PI at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate).

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

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

Samples retained for further use are registered in the AstraZeneca Biobank system during the entire lifecycle.

5.7.11 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.

Tumour sample for tumour *BRCA* testing and blood sample for germline *BRCA* testing: As collection of these biological materials is an integral part of the study, then the patient is withdrawn from further study participation.

Tumour sample for central HRR testing using the Lynparza HRR Assay:

- If the central *BRCA* test identifies the patient as carrying *BRCA*m disease, then the patient will remain in the study. The sample provided for HRR testing 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.
- If the central *BRCA* test identifies the patient as carrying *BRCA*wt disease, as collection of this biological material is an integral part of the study, then the patient is withdrawn from further study participation.

Exploratory analysis samples: archival tumour/ tumour tissue sample (biopsy samples) for exploratory analysis and blood samples for ctDNA analysis: As collection of these biological materials is an optional part of the study, then the patient may continue in the study.

The PI:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca or designated Contract Research Organisation (CRO)
- 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 of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

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

5.8 Blood volume

The volume of blood that will be drawn from each patient will vary, dependent upon the length of time that the patient remains in the trial and on treatment. However the volume of blood to be drawn from each patient during screening and up to Day 29 should not exceed 50 mL.

The total volume of blood to be drawn from each patient in the study, assuming they complete screening, 6 months of treatment, a treatment discontinuation visit and the 30-day follow-up visit, should not exceed 139 mL.

Safety laboratory assessments will be performed locally at the discretion of the investigator according to routine local clinical practice and in line with the prescribing information or the IB as applicable based on country specific marketing authorisation status, where olaparib is approved, at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore patient to site-specific change and the above is for guidance only.

Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments.

The estimated total volume of blood that will be drawn from each patient in this study is shown in Table 5.

Table 5 Estimated maximum volume of blood to be drawn from each patient based on 6 months of treatment

Assessment		**Sample volume (mL)**	**Screening** No. of samples	**Month 1 (Including day 29)** No. of samples	**Months 2-6** No. of samples	**Treatment discontinuation visit and 30 day follow-up visit** No. of samples	**Total vol. (mL)**
Safety	Clinical chemistry (locally considered and assessed)	5	1	2	5	2	**50**
	Haematology (locally considered and assessed)	5	1	2	5	2	**50**
Whole Blood sample: Prospective BRAC*Analysis*® test for patients with tumour *BRCA*m status		7	1				**7**
Serum pregnancy test		Site dependent	Site may use urine	Site may use urine			
Blood sample for CA-125 (locally considered and assessed)		2	1				**2**
Blood sample for plasma / ctDNA analysis*		10		3			
Total volume (mL)			**19**	**50**	**50**	**20**	**139**

*: Optional and subject to specific informed consent. Only for patients with s*BRCA*m and HRRm ovarian cancer. If sBRCAm status is not known at Day 29, these samples can be taken at a later study visit.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product,

whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., 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 ‘Additional Safety Information’ to the Clinical Study Protocol.

6.3 Adverse events of special interest

Adverse events of special interest (AESI) for olaparib are events of scientific and medical interest specific to the further understanding of olaparib’s safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI may be serious or non-serious. Adverse Events of Special Interest for olaparib are the important potential risks of MDS/AML, new primary malignancies (other than MDS/AML) and pneumonitis type events.

Any event of MDS/AML, new primary malignancy (other than MDS/AML), or pneumonitis should be reported to AstraZeneca Patient Safety whether it is considered a non-serious AE (e.g. non-melanoma skin cancer) or SAE, and regardless of investigator’s assessment of causality. These adverse events must be reported according to the timelines for reporting an SAE (see Section 6.4) to allow timely safety monitoring. A questionnaire will be sent to any investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study there may be other events identified as AESIs that require the use of a

questionnaire to help characterise the event and gain a better understanding regarding the relationship between the event and study treatment.

6.4 Recording of adverse events

6.4.1 Time period for collection of adverse events

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

*Exception: In screening part 1 only SAEs related to study procedures must be reported (AEs do not require reporting). From screening Part 2 onwards - all AEs/SAEs must be reported.

In cases where any transfusions to manage anaemia and or thrombocytopenia are needed, these should be recorded with date, type and units given.

6.4.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the time of the 30 day follow-up, must be followed up by the investigator through to resolution, and whilst the database is open should be recorded on the database.

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

6.4.3 Adverse events after the 30 day follow-up period

For Pharmacovigilance purposes and characterisation of events of special interest, any case of MDS/AML or new primary malignancy, as well as pneumonitis occurring after the 30 day follow up period should be reported as SAE (or AE for non-melanoma skin cancers, if at least one of the criteria for SAE is not met, see Section 6.2) to AstraZeneca Patient Safety regardless of investigator's assessment of causality. A Questionnaire will be sent to any investigator reporting MDS/AML or new primary malignancy or pneumonitis as an aid to provide detailed information on the case.

At any time after a patient has completed the study, if an investigator learns of any SAE including death, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AstraZeneca, Patient Safety.

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut-off and/or post study completion then all SAEs must continue to be collected and reported to Astra Zeneca Patient Safety within the usual timeframe.

Otherwise after study treatment completion (i.e., after any scheduled post treatment follow-up period has ended), there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow-up period (30 days).

6.4.4 **Variables**

The following variables will be collect for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Max CTCAE grade and changes in CTCAE grade
- 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 serious AE
- Date Investigator became aware of serious AE
- AE is serious due to (provide all seriousness criteria applicable)
- Date of hospitalisation (if applicable)
- Date of discharge (if applicable)
- Probable cause of death (if applicable)
- Date of death (if applicable)
- Autopsy performed (yes or no; if yes provide report) (if applicable)
- Causality assessment in relation to study procedure(s)
- Description of serious AE.

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.1. 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 unless it meets the criteria shown in Section 6.2. 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 when it satisfies the criteria shown in Section 6.2.

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

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

6.4.5 Causality collection

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

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

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

6.4.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.4.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.4.8 Disease progression

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

6.4.9 New cancers

The development of a new primary cancer (including skin cancer) should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 6.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

6.4.10 Lack of efficacy

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

6.4.11 Deaths

All deaths that occur in screening Part 1 related to study procedures should be reported as a SAE.

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

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the 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 6.2 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'Death eCRF'.
- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca within the usual timeframes.

6.5 Reporting of serious adverse events

In screening Part 1, only SAEs related to study procedures must be reported. From screening Part 2 onwards, all SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives immediately, but **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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform designated AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

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

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

The reference document for definition of expectedness/listedness is the IB or the Prescribing Information (Appendix G) as applicable based on country specific marketing authorisation status for the AstraZeneca drug.

6.6 Overdose

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

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose.

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

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

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

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.5. For other overdoses, reporting must occur within 30 days.

6.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.7.1 Maternal exposure

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

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

If any pregnancy occurs during the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **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 calendar days for SAEs (see Section 6.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

6.7.2 Paternal exposure

Not applicable.

6.8 Management of IP related toxicities, dose interruptions and dose reductions

Study treatment may be temporarily interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea, and anaemia and dose reduction can be considered. The recommended dose reduction is to 200 mg twice daily (equivalent to a total daily dose of 400 mg). If a further final dose reduction is required, then reduction to 100 mg twice daily (equivalent to a total daily dose of 200 mg) could be considered. In cases where any transfusions to manage anaemia and or thrombocytopenia are needed, these should be recorded with date, type and units given.

6.9 Study governance and oversight

Not applicable.

6.9.1 Steering Committee

Not applicable.

6.9.2 Data Monitoring Committee

Not applicable.

6.9.3 Scientific Advisory Committee

A scientific advisory committee will be established as part of the study to provide guidance on study conduct and interpretation, chaired by the PI and including key investigators and optional external experts as needed. This committee will be facilitated by AstraZeneca.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib to the Investigator as white, size 0 capsules (Appendix G 'Prescribing Information').

Investigational product	Dosage form and strength
Olaparib	Capsule – 50 mg

a Descriptive information for olaparib can be found in the Investigator's Brochure or the Prescribing Information as applicable based on country specific marketing authorisation status

7.2 Dose and treatment regimens

Olaparib capsules will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle will contain 120 capsules and 4 bottles will be dispenses for a 4 weekly visit, with a 2-day overage.

Patients will be administered olaparib capsules orally at a dose of 400 mg twice daily.

Eight 50 mg olaparib capsules should be taken at the same time each day approximately 12 hours apart with approximately 240 mL of water.

The olaparib capsules should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib capsules can be taken with a light meal/snack (e.g., 2 pieces of toast or a couple of biscuits).

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

There is no maximum duration for taking olaparib. Patients should continue to receive olaparib until disease progression as assessed by the investigator or as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 3.9.

7.3 Labelling

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

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

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

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

7.5 Compliance

The administration of investigational product should be recorded in the appropriate sections of the Case Report Form.

Patients should be given clear instructions on how and when to take olaparib. Patients will self-administer olaparib. Study site staff will make capsule counts at regular intervals during treatment. Compliance will be assessed by the capsule count and the information will be

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

Patients must return all containers and any remaining IP capsules at the end of the study.

7.6 Accountability

The IP provided for this study will be used only as directed in the study protocol.

The study personnel will account for all IP dispensed to and returned from the patient.

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

7.7 Concomitant and other treatments

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy, radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication. Hormone replacement therapy (HRT) is acceptable.

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

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

Any medications (with the detailed exceptions) which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the investigator and according to olaparib prescribing information where approved and applicable, providing the medications, the doses, dates and reasons for administration are recorded.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded. This includes any blood transfusions.

The reasons for the use, doses and dates of treatment should be recorded in the patient’s medical records and appropriate sections of the eCRF.

All medications (prescriptions or over the counter medications) continued at the start of study or started during the study or until 30 days from the end of the last IP dose and different from the study medication must be documented.

Combination of olaparib with vaccines or immunosuppressant agents has not been studied. Therefore, caution should be taken if these drugs are co-administered with olaparib and patients should be closely monitored.

Clinical studies to evaluate the impact of known CYP3A inhibitors and inducers have not been conducted and it is therefore recommended that known strong inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or inducers (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) of these isozymes should be avoided with olaparib.

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

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

The potential for olaparib to induce CYP3A, CYP1A2, CYP2B6, CYP2C9, CYP2C19 and P-gp is unknown and it cannot be excluded that olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib.

In vitro olaparib may be an inhibitor of P-gp and is an inhibitor of BRCP, OATP1B1, OCT1 and OCT2. It cannot be excluded that olaparib may increase the exposure to substrates of P-gp (e.g., statins, digoxin, dabigatran, colchicine), BRCP (e.g., methotrexate, rosuvastatin and sulfasalazine), OATP1B1 (e.g., bosentan, glibenclamide, repaglinide, statins, and valsartan), OCT1 (e.g., metformin) and OCT2 (e.g., serum creatinine). In particular, caution should be exercised if olaparib is administered in combination with any statin.

Patients who are taking warfarin or acenocoumarol may participate in this trial; however, it is recommended that prothrombin time (international normalised ratio [INR] and activated partial thromboplastin time [APTT]) be monitored at baseline if patients are on anticoagulation at enrolment and repeat as per local guidelines for the anticoagulation treatment after start of olaparib and when clinically indicated. For AEs of haemorrhage coagulation status and relevant monitoring of laboratory results is recommended.

From screening Part 2 onwards, should a patient develop nausea, vomiting and / or diarrhoea, then these symptoms should be reported as AEs and appropriate treatment of the event given.

7.7.1 Surgery and palliative radiotherapy

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

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Olaparib should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Olaparib should be restarted within 2 weeks as long as any bone marrow toxicity has recovered.

7.7.2 Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on olaparib. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 2 weeks prior to beginning olaparib or if disease progression is recorded, then olaparib could be continued alongside bisphosphonates, denosumab or corticosteroids as above if the in the investigator's assessment the patient would continue to benefit from further olaparib therapy .

7.7.3 Subsequent therapies for cancer

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anti-cancer therapies including access to other PARP inhibitors or investigational drugs will be collected and included in the exploratory assessments of OS.

7.7.4 Other concomitant treatment

Other medication other than that described above, 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 Case Report Form.

7.8 Post Study Access to Olaparib

After the end of the study, patients still on study therapy at that time will continue to receive olaparib outside the study until they continue to derive clinical benefit from treatment in the view of the investigator and no other criteria for treatment discontinuation are met.

8. STATISTICAL CONSIDERATIONS

Analyses will be performed by AstraZeneca or its representatives.

A comprehensive SAP will be prepared and any subsequent amendments will be documented, with final amendments completed prior to the start of the first patients on the study. Data will be summarised for all patients who have received at least one dose of olaparib and will be presented separately for patients with *BRCA*m and *BRCA*-independent HRRm ovarian cancer.

8.1 Sample size estimate

Patients with s*BRCA*m disease

Based on the expected proportion of s*BRCA*m disease among all patients with *BRCA* mutated disease, as outlined in section 1.1.2, the study is aiming to recruit at least 50 patients with s*BRCA*m disease.

Assuming a median PFS value of 11.2 months (as observed in the phase 2 maintenance study), and a data cut off at 60% maturity, 30 progression or death events are expected from 50 patients with s*BRCA*m disease. Assuming 23 months non-linear recruitment, in the s*BRCA*m cohort these 30 progression or death events are expected to occur approximately 32 months after first subject is enrolled in the study (FSI).

All patients with *BRCA*m disease

The sample size of approximately 250 patients is driven by the need to understand patterns of olaparib use across multiple countries with the capsule formulation and across various subgroups and the primary analysis will be performed after the accumulation of 150 progression or death events which corresponds to 60% maturity. Assuming a median PFS value of 11.2 months and a data cut off at 60% maturity with approximately 23 months of non-linear recruitment 150 progression or death events are expected to occur approximately 32 months after first subject is enrolled in the study (FSI).

HRRm exploratory cohort

It is expected that approximately 450 patients with *BRCA*wt status will be screened using the Lynparza HRR Assay. Assuming that approximately 5% of patients with *BRCA*wt disease screened in the study will carry a qualifying genetic alteration in any of the 13 genes involved in the HRR pathway (excluding *BRCA1* and *BRCA2*), it is estimated that approximately 25 patients will be included in the HRRm cohort before the target number of 250 patients with *BRCA*m disease is reached.

8.2 Definitions of analysis sets

Table 6 gives a summary of outcome variables and analysis populations.

Table 6 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data	
- Primary: PFS	Full

Outcome Variable	Populations
- Secondary: OS, PFS2, TFST, TSST, TDT, symptom/QoL endpoints	Full
Demography	Full
Safety Data	
- Adverse Events	Safety
- Lab measurements	Safety
- Vital Signs	Safety

Note: TFST: time to first subsequent therapy or death; TSST: time to second subsequent therapy or death; TDT: time to olaparib discontinuation or death; PFS2: Investigator assessed second progression; OS: Overall Survival.

8.2.1 Full analysis set

The full analysis set (FAS) includes all patients who have been assigned olaparib (all enrolled patients as an intention to treat analysis set). All efficacy analyses will be based on the FAS.

8.2.2 Safety analysis set

The safety analysis set comprises all patients who received at least 1 dose of olaparib. All safety analyses will be based on the safety analysis set.

8.2.3 PK analysis set

Not applicable.

8.2.4 PRO analysis set

PRO analyses will be based on the FAS, with additional exclusion criteria, excluding:

- Patients who do not have any evaluable baseline data
- Patients who do not have any evaluable post-baseline data.

8.3 Outcome measures for analyses

8.3.1 Calculation or derivation of efficacy variable(s)

At each visit patients will be programmatically assigned a visit response of CR, PR, SD, PD, NE based on RECIST 1.1 guidelines or other methods depending on the status of their disease compared to baseline and previous assessments, based on the investigator assessment.

8.3.2 Primary endpoint

PFS is defined as the time from enrolment until the date of objective radiological disease progression (assessed via RECIST 1.1) or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to disease progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last

evaluable efficacy assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable assessment. Given the scheduled visit assessment scheme, two missing visits will equate to more than 26 weeks since the previous RECIST 1.1 assessment, allowing for early and late visits. If the patient has no evaluable visits or does not have a baseline assessment they will be censored at day 1 unless they die within two visits of baseline (25 weeks allowing for visit window).

The PFS time will always be derived based on scan/assessment dates not visit dates. Assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the assessment/scan dates of the component that triggered the progression.
- When censoring a patient for PFS the patient will be censored at the latest of the assessment/scan dates contributing to a particular overall visit assessment.

Overall visit assessments will be determined for each assessment (scheduled or unscheduled) and will contribute to the derivation of PFS.

Objective radiological progression is defined as at least a 20% increase in the sum of the diameters of the target lesions (compared to previous minimum sum) and an absolute increase of > 5 mm, or an overall non-target lesion assessment of progression or a new lesion.

8.3.3 Secondary endpoints

Overall Survival

Overall survival is defined as the time from the date of enrolment in the study until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made in the week following the DCO for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO.

Time from enrolment to second progression (PFS2)

Time from enrolment to second progression is defined as the time from the date of enrolment to the earliest of the progression event subsequent to that used for the primary variable PFS or death. The date of second progression will be recorded by the investigator and defined according to local standard clinical practice and may involve any of objective radiological, symptomatic, CA-125 progression or death. Second progression status will be reviewed every 12 weeks following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a

second disease progression, i.e., censored at the last assessment for progression date if the patient has not had a second progression or death.

Time to first subsequent anti-cancer therapy or death (TFST)

As a supportive summary to PFS, time to start of first subsequent anti-cancer therapy or death will be assessed. Time to first subsequent therapy or death is defined as the time from the date of enrolment to the earlier of first subsequent therapy start date, or death date. Any patient not known to have had a further subsequent therapy or death will be censored at the last known time to have not received subsequent anti-cancer therapy.

Time to study treatment discontinuation or death (TDT)

Time to study treatment discontinuation or death (TDT) will be assessed. TDT is defined as the time from the date of enrolment to the earlier of the date of study treatment discontinuation or death. Any patient not known to have died at the time of analysis and not known to have discontinued study treatment will be censored based on the last recorded date on which the patient was known to be alive.

Time to second subsequent chemotherapy or death (TSST)

As a supportive summary to PFS2, time to start of second subsequent chemotherapy or death (TSST) will be assessed. Time to second subsequent chemotherapy or death is defined as the time from the date of enrolment to the earlier of the date of second subsequent chemotherapy start date, or death date. Any patient not known to have had a further second subsequent therapy or death will be censored at the last known time to have not received second subsequent chemotherapy.

8.3.4 Calculation or derivation of health-related quality of life variables

FACT-O

Patient-reported health-related quality of life (HRQoL) will be assessed using the FACT-O questionnaire (Appendix H). The FACT-O is composed of the following sub-scales: physical, social/family, emotional, and functional well-being as well as the additional concerns scales consisting of specific ovarian cancer symptoms.

The main end point for health-related quality of life analysis will be the Trial Outcome Index (TOI), an established single targeted index derived from the FACT-O questionnaire and it is considered to target the most relevant symptoms together with function and physical well-being and can be directly related to signs and symptoms and AEs. The TOI is composed of the following scales of the FACT-O: physical and functional well-being and additional concerns.

Data relating to the FACT-O will be self-reported through patient questionnaires according to the study plan. Patients will be asked to report their health-related quality of life over the course of the previous 7 days. All patients will be asked to complete the FACT-O. The FACT-O questionnaire will be administered per study schedule (Table 2 and Table 3). In

addition, Quality of Life questionnaire will be collected at the discontinuation of study treatment visit 8 and 30 days post last dose. Patients who had disease progression according to RECIST 1.1 will complete the questionnaires during the 12 weekly survival follow up either in person or over the phone.

The Trial Outcome Index (TOI) score will be derived from the sum of the scores of the 25 items included in the physical well-being (7 items), functional well-being (7 items), and ovarian cancer subscale (11 items) of the FACT-O questionnaire version 4. The total FACT-O score will also be calculated which is made up of the sum of the individual subscale scores: physical well-being (PWB), social well-being (SWB), emotional well-being (EWB) and functional well-being (FWB), and the ovarian cancer subscale (Additional Concerns).

The scores will be derived in accordance with the FACT-O scoring manual. A number of items are negatively stated and need to be reversed by subtracting the response from "4". The scoring manual identifies that the following items need to be reversed prior to summarizing: GP1-7, GE1, GE3-6, O1-3, C2, and B5. After reversing proper items, scores are summarised and multiplied by the number of items in the domain. For each subscale, if less than 50% of the subscale items are missing, the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscale. If at least 50% of the items are missing, that subscale also will be treated as missing. The reason for any missing assessment will be identified. If data are missing at random, the above techniques will be used. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimised. The TOI score ranges from 0-100 and the FACT-O from 0-152. For all Functional Assessment of Chronic Illness Therapy (FACIT) scales and symptom indices, a higher score indicates a higher HRQoL.

The actual change from baseline in TOI score will be derived for each visit where there is available data. For example; at visit X, the calculation will be (TOI score at visit X- baseline TOI score). Actual change from baseline for the individual domain scores will be calculated in a similar way.

A change of at least 10 points in TOI score will be considered as a clinically relevant or a minimally important difference.

The threshold for a clinically important deterioration is outlined below (Table 7):

Table 7 Health-Related QoL

Score	Change from baseline	Visit response
TOI	≥ +10	Improved
	≤ -10	Worsened
	Otherwise	No change

Best Overall TOI improvement (in absence of starting any subsequent cancer therapy) will be defined as a change from baseline in the TOI of + 10 points or more sustained for at least 28 days, the denominator consisting of a subset of the efficacy population who have baseline TOI. It will be derived as the best symptom improvement response the patient achieved, based on evaluable QoL data collected from enrolment up to the earliest of starting any subsequent cancer therapy or death. Therefore, at the conclusion of the trial, the following criteria, will be used to assign a best overall score response based on the individual visit responses (Table 8).

Table 8 Health-Related Quality of Life: Change rates - overall score.

Best Overall TOI score response	Criteria
Improved	Two visit responses of "improved" a minimum of 28 days apart without an intervening visit response of "worsened"
No change	Does not qualify for overall score response of "improved". Two visit responses of either "no change" or "improved and "no change" a minimum of 28 days apart without an intervening visit response of "worsened"
Worsened	Does not qualify for overall score response of "improved" A visit response of "worsened" without a response of "improved" or "no change" within 28 days.
Other	Does not qualify for one of the above.

A TOI improvement rate (in the absence of subsequent cancer therapy) will be calculated as the proportion of all analysed patients with a best overall score response of improved. In the calculation of the proportion of patients that have a response of Improved, No Change or Worsened, the denominator used in the calculation will use the number evaluable for that individual TOI domain score at baseline.

FACIT-Fatigue

The scores will be derived in accordance with the FACIT-Fatigue Scoring Guidelines. A number of items are negatively stated and need to be reversed by subtracting the response from "4". The scoring manual identifies that the following items need to be reversed prior to summarising: HI7, HI12, An1, An2, An3, An4, An8, An12, An14, An15 and An16. After reversing proper items, scores are summarised and multiplied by the number of items in the domain (x13) and divided by number of items answered to obtain the Fatigue subscale score.

ORZORA QoL Additional Items Questionnaire

As no scoring guidelines exist for these new questions, the number and percentage of patients giving each response ("Not at all", "A little bit", "Somewhat", "Quite a bit", "Very much") will be summarised.

FLIE

The Functional Living Index-Emesis (FLIE) scores will be derived. - Full details will be provided in the Statistical Analysis Plan.

8.3.5 Calculation or derivation of safety variable(s)

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, and vital signs. These will be collected for all patients. The number of patients experiencing each AE (based on Medical Dictionary for Regulatory Activities [MedDRA] preferred term) will be summarised by CTCAE grade.

8.3.6 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 investigational product due to adverse events (DAEs). Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. 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.

8.3.7 Exploratory endpoints

Descriptive analyses will be performed for exploratory endpoints. Specific analyses will be described in the Statistical Analysis Plan.

8.4 Methods for statistical analyses

Data will be summarised for all patients who have received at least one dose of olaparib and will be presented separately for the *BRCA*m and HRRm patients.

The primary analysis will be performed at 60% maturity, that is, at the time of accrual of 150 progression or death events in the 250 *BRCA*m patients, with assessment of progression based on RECIST 1.1guidelines. It is expected that the cohort of patients with s*BRCA*m disease will comprise at least 50 patients at the time of this analysis, and that 30 progression/death events will have occurred in this cohort.

Subgroup analyses will be performed on the g*BRCAm* group separately.

8.4.1 Analysis of the primary variable

PFS will be analysed when approximately 150 progression events among patients with *BRCA* mutated ovarian cancer have occurred in the study (60% maturity). At this point, it is expected that 30 progression events (60% maturity) would have occurred in the cohort of at least 50 patients with s*BRCA*m disease. PFS analyses will be performed in the cohort of patients with s*BRCA*m disease and all *BRCA*m patients, both assessed according to RECIST 1.1 guidelines, to address the co-primary objectives of the study.

Kaplan-Meier (KM) plots of PFS will be presented for the cohort of patients with s*BRCA*m disease and for all patients with *BRCA*m disease. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (progression or death) will be provided along with median PFS and 95% confidence intervals.

The analyses on PFS will be based on investigator assessments according to RECIST 1.1 guidelines, and using all scans regardless of whether they were scheduled or not. The estimated PFS rates at 6 months, 12 months and 24 months will be summarised (using the KM curves) for the cohort of patients with s*BRCA*m disease and for all patients with *BRCA*m disease.

The number of patients prematurely censored will be summarised together with baseline prognostic factors of the prematurely censored patients. A patient is defined as prematurely censored if they had not progressed and the latest scan prior to DCO was more than 1 scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date.

The analyses of PFS will be repeated on the exploratory HRRm cohort.

8.4.2 Analysis of the secondary variable(s)

All time to event endpoints (OS, PFS2, TFST, TSST, and TDT) will be described as for PFS in the subset of patients with s*BRCA*m disease, and for all patients with *BRCA*m disease. A summary of PFS2 and OS will be produced at the time of the PFS data cut off. Descriptive analyses will be performed on all QoL endpoints, using frequency distribution for categorical endpoints and means and corresponding 95% confidence intervals for continuous endpoints. The analyses of OS will be repeated on the exploratory HRRm cohort. Further details will be provided in the Statistical Analysis Plan.

Safety data will be summarised and reported for all patients with *BRCA*m, patients with s*BRCA*m and patients with HRRm ovarian cancer.

8.4.3 Subgroup analysis

Among patients with *BRCA*m disease, subgroup analyses will be presented, as described for the primary analysis of PFS, to assess the consistency of olaparib effect across potential or expected prognostic factors.

The following subgroups of the FAS may be summarised.

- Response to previous platinum chemotherapy (CR vs PR)
- Time to disease progression on last platinum based chemotherapy received prior to first dose of olaparib (6 – 12 months / > 12 months)
- Measurable versus non-measurable disease at baseline
- *BRCA* mutation type, e.g. g*BRCA*; *BRCA1, BRCA2* or *BRCA1/2* (both)
- Age at enrolment (<65 vs ≥65 years old)
- Region
- Prior PARP inhibitor use
- Family history
- Prior bevacizumab use.

Other baseline variables may also be assessed if there is clinical justification. Further explorations will be undertaken for patient characteristics within germline and somatic *BRCA* mutated disease groups. Details will be provided in the Statistical Analysis Plan.

8.4.4 Interim analysis

No formal statistical interim analyses for PFS are planned for this trial.

8.4.5 Exploratory analysis (if applicable)

Exploratory translational science endpoints

Full statistical methods for biomarker exploratory endpoints will be defined in a separate translation science analysis plan. Biomarker data will be summarised descriptively using tables and plots. If the data is available at the time of developing the CSR then the biomarker data will be included in the CSR. Otherwise the biomarker data will be reported in a separate addendum to the CSR (if applicable). Further details on the data summaries and plots for the biomarker data for the CSR will be provided in the SAP.

8.5 Training of study site personnel

Before the first patient is entered into the study, a designated AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC and/or any electronic PROs 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).

8.6 Monitoring of the study

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the 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 (e.g., 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 centre needs information and advice about the study conduct.

8.6.1 Source data

Refer to the Clinical Study Agreement for location of source data.

8.6.2 Study agreements

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

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

8.6.3 Archiving of study documents

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

8.7 Study timetable and end of study

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

The study is expected to start in Q3 2015 and to end by Q2 2018.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (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.

8.8 Data management by AstraZeneca

Data management will be performed by an AstraZeneca representative, according to the Data Management Plan.

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

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Clinical Informatics Plan and Data Quality Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Plans will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

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

Serious Adverse Event (SAE) reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data management of genotype data

Exploratory genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this exploratory genetic research may be reported in the CSR.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

Management of external data

Data from external providers (e.g. central laboratories) will be validated as appropriate to ensure it is consistent with the clinical data and included in the final database.

In the case of biomarker (tumour tissue or blood for exploratory analyses) data, the results of any analyses will not be recorded in the database, but information relating to the processing of the sample, including the original date of biopsy (historical tumour tissue sample and the actual date the sample(s) were collected) will be recorded in the eCRF and database.

9. ETHICAL AND REGULATORY REQUIREMENTS

9.1 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.

9.2 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.

9.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The Informed Consent Form will address the donation of tissue and blood samples for *BRCA* testing, tissue sample for HRR testing, as well as optional tissue samples for exploratory analysis and optional blood samples for ctDNA analysis.

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 before enrolment of any patient into the study.

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

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

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

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

For the US and Canada, *may also be applicable to other countries:*

Each PI is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the PI so that he/she can meet these reporting requirements.

9.4 Informed consent

The Principal Investigator(s) at each centre 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.

9.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator, the Principal Investigator and AstraZeneca or designated CRO.

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 or designated CRO will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 9.6.

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

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

9.6 Audits and inspections

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

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Clinical Study Protocol Appendix A	
Drug Substance	Olaparib
Study Code	D0816C00012
Edition Number	3.0
Date	22 July 2016
Protocol Dated	22 July 2016

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

An Open Label, Single Arm, Multicentre Study to Assess the Clinical Effectiveness and Safety of Lynparza (Olaparib) Capsules Maintenance Monotherapy in Platinum Sensitive Relapsed somatic or germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy (ORZORA)

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

I agree to the terms of this study protocol edition 3.

AstraZeneca Research and Development site representative

PPD

AstraZeneca
Global Medical Affairs, Oncology
Academy House
132 Hills Rd, Cambridge
Cambridgeshire, CB2 1PG
United Kingdom

PPD

ASTRAZENECA SIGNATURE(S)

An Open Label, Single Arm, Multicentre Study to Assess the Clinical Effectiveness and Safety of Lynparza (Olaparib) Capsules Maintenance Monotherapy in Platinum Sensitive Relapsed somatic or germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy (ORZORA)

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

I agree to the terms of this study protocol edition 3.

AstraZeneca Research and Development site representative

PPD

AstraZeneca
R&D, Global Medicines Development
The DaVinci Building - Melbourn Science Park
Cambridge Road, Royston
Hertfordshire, SG8 6HB
United Kingdom

PPD

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

An Open Label, Single Arm, Multicentre Study to Assess the Clinical Effectiveness and Safety of Lynparza (Olaparib) Capsules Maintenance Monotherapy in Platinum Sensitive Relapsed somatic or germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy (ORZORA)

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

I agree to the terms of this study protocol edition 3. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Site No.: PPD

Signature:

Professor Sandro Pignata
National Cancer Institute of Naples
Via Mariano Semmola
80131 Naples, Italy

Date
(Day Month Year)

PPD

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

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Clinical Study Protocol Appendix B	
Drug Substance	Olaparib
Study Code	D0816C00012
Edition Number	1
Date	26 February 2015

Appendix B
Additional Safety Information

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

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the patient'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

Out-patient 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 patient 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 jeopardise the patient 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 should 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 patient 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.

Clinical Study Protocol Appendix C	
Drug Substance	Olaparib
Study Code	D0816C00012
Edition Number	1
Date	26 February 2015

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

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Clinical Study Protocol Appendix D	
Drug Substance	Olaparib
Study Code	D0816C00012
Edition Number	1
Date	26 February 2015

Appendix D
Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** 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.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

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 are met.

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

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

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

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

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

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

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

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

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

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

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

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]

  - If there is no significant change no action is required

  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described is Section 4.2 of this Appendix

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

7. 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 E

Drug Substance	AZD2281/Olaparib
Study Code	D0816C00012
Edition Number	2
Date	01 September 2015

Appendix E
Acceptable Birth Control Methods

1. ACCEPTABLE BIRTH CONTROL METHODS

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

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

Acceptable Non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must continue for the total duration of study treatment and for at least 1 month after the last dose. Periodic abstinence (e.g., calendar ovulation, symptothermal post ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom.
- Intrauterine device [IUD] PLUS male condom. Provided coils are copper-banded.

Acceptable hormonal methods:

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

Clinical Study Protocol Appendix F	
Drug Substance	Olaparib
Study Code	D0816C00012
Edition Number	2
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Appendix F
Guidance of Evaluation of Objective Tumour Response Using Modified RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

1. INTRODUCTION

This appendix details the implementation of modified RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the CCI study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

1. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Patients with measurable disease and/or non measurable and/or no evidence of disease assessed at baseline by CT/MRI will be entered in this study. RECIST 1.1. has been modified to allow the assessment of progression due to new lesions in patients with no evidence of disease at base-line.

Measurable:

A lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions**
- Skin lesions assessed by clinical examination
- Brain metastasis

* Nodes with <10mm short axis are considered non-pathological and should not be recorded or followed as NTL.

**Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as Non-Target Lesions (NTL) at baseline and followed up as part of the NTL assessment.

Special Cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient; these should be selected as target lesions.

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

Non-Target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

2. METHODS OF ASSESSMENT

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Table 1 Summary of Methods of Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest x-ray	X-ray, Chest x-ray
		Ultrasound
		Bone Scan
		FDG-PET

3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D0816C00012 study it is recommended that CT examinations of the chest*, abdomen and pelvis will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (i.v.) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

- *Chest, abdomen and pelvis CT/MRI scans should be performed at baseline.
- *In those patients with thoracic lesions or upper abdomen lymphadenopathy identified at baseline assessment, chest, abdomen and pelvis should be performed at follow-up.
- *In those patient with no disease present in the chest and no upper abdomen lymphadenopathy then follow-up is by abdomen and pelvis only.

3.2 Clinical examination

In the D0816C00012 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

3.3 X-ray

3.3.1 Chest X-ray

In the D0816C00012 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

3.3.2 Plain X-ray

In the D0816C00012 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4 Ultrasound

In the D0816C00012 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

In the D0816C00012 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

3.6 Tumour markers

In the D0816C00012 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

In this study the following marker(s) CA-125 are being collected for separate analysis. However, the results will not contribute to tumour response based on RECIST 1.1 assessment.

3.7 Cytology and histology

In the D0816C00012 study histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D0816C00012 study isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

3.9 FDG-PET scan

In the D0816C00012 study FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI

assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

3. TUMOUR RESPONSE EVALUATION

Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before randomisation, and ideally should be performed as close as possible to the start of study treatment. Follow-up assessments will be performed every 12 weeks (±1 week), up to 72 weeks, then every 24 weeks (±1 week) relative to date of randomisation, until objective disease progression as defined by modified RECIST 1.1. See Table 3: Study Schedule from Study Protocol for further information. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

4.2 Target lesions (TL)

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.

- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.

- If a TL splits into two or more parts, then record the sum of the diameters of those parts.

- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.

- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL.

Table 2 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.

Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response

4.3 Non-target lesions (NTL)

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 3 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL
Progression (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

To achieve ‘unequivocal progression’ on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

4.4 New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

4.6 Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 4.

Table 4 Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/Non PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NA	NA	No	NED

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NED = no evidence of disease, NA = not applicable (only relevant if there were no TL/NTL at baseline).

4. REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45 (2009) 228-247

AstraZeneca

Clinical Study Protocol Appendix G	
Drug Substance	Olaparib
Study Code	D0816C00012
Edition Number	1
Date	26 February 2015

Appendix G
Prescribing Information

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 50 mg of olaparib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
White, opaque, size 0 hard capsule, marked with "OLAPARIB 50 mg" and the AstraZeneca logo in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

4.2 Posology and method of administration

Treatment with Lynparza should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Patients must have confirmation of a breast cancer susceptibility gene (*BRCA*) mutation (either germline or tumour) before Lynparza treatment is initiated. *BRCA* mutation status should be determined by an experienced laboratory using a validated test method (see section 5.1).

There are limited data in patients with somatic *BRCA*-mutated tumours (see section 5.1).

Genetic counselling for patients with *BRCA* mutations should be performed according to local regulations.

Posology

The recommended dose of Lynparza is 400 mg (eight capsules) taken twice daily, equivalent to a total daily dose of 800 mg.

Patients should start treatment with Lynparza no later than 8 weeks after completion of their final dose of the platinum-containing regimen.

It is recommended that treatment be continued until progression of the underlying disease. There are no data on retreatment with Lynparza following subsequent relapse (see section 5.1).

Missing dose
If a patient misses a dose of Lynparza, they should take their next normal dose at its scheduled time.

Dose adjustments
Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea, and anaemia and dose reduction can be considered (see section 4.8).

The recommended dose reduction is to 200 mg twice daily (equivalent to a total daily dose of 400 mg).

If a further final dose reduction is required, then reduction to 100 mg twice daily (equivalent to a total daily dose of 200 mg) could be considered.

Elderly patients
No adjustment in starting dose is required for elderly patients. There is limited clinical data in patients aged 75 or over.

Patients with renal impairment
The effect of renal impairment on exposure to Lynparza has not been studied. Lynparza can be administered in patients with mild renal impairment (creatinine clearance > 50 ml/min).

There is limited data in patients with moderate renal impairment (creatinine clearance < 50 ml/min) or severe renal impairment (creatinine clearance < 30 ml/min), and safety and efficacy have not been established. Therefore, Lynparza is not recommended for use in these renally impaired patients.

Lynparza may only be used in patients with moderate or severe renal impairment if the benefit outweighs the potential risk, and the patient should be carefully monitored for renal function and adverse events.

Patients with hepatic impairment
The effect of hepatic impairment on exposure to Lynparza has not been studied. Therefore, Lynparza is not recommended for use in patients with hepatic impairment (serum bilirubin greater than 1.5 times upper limit of normal), as safety and efficacy have not been established.

Non-Caucasian patients
There are limited clinical data available in non-Caucasian patients. However, no dose adjustment is required on the basis of ethnicity (see section 5.2).

Patients with performance status 2 to 4
There are very limited clinical data available in patients with performance status 2 to 4.

Paediatric population
The safety and efficacy of Lynparza in children and adolescents has not been established.
No data are available.

Method of administration

Lynparza is for oral use.

Due to the effect of food on olaparib absorption, patients should take Lynparza at least one hour after food, and refrain from eating preferably for up to 2 hours afterwards.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Breast-feeding during treatment and 1 month after the last dose (see section 4.6).

4.4 Special warnings and precautions for use

Haematological toxicity
Haematological toxicity has been reported in patients treated with olaparib, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropaenia, thrombocytopaenia and lymphopaenia. Patients should not start treatment with Lynparza until they have recovered from haematological toxicity caused by previous anticancer therapy (haemoglobin, platelet, and neutrophil levels should be within normal range or CTCAE grade 1). Baseline testing, followed by monthly monitoring, of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment.

If a patient develops severe haematological toxicity or blood transfusion dependence, treatment with Lynparza should be interrupted and appropriate haematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of Lynparza dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended.

Myelodysplastic syndrome/Acute Myeloid Leukaemia
Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML) have been reported in a small number of patients who received Lynparza alone or in combination with other anti-cancer drugs; the majority of cases have been fatal. The duration of therapy with olaparib in patients who developed MDS/AML varied from < 6 months to > 2 years. The cases were typical of secondary MDS/cancer therapy-related AML. All patients had potential contributing factors for the development of MDS/AML; the majority of cases were in g*BRCA* mutation carriers and some of the patients had a history of previous cancer or of bone marrow dysplasia. All had received previous platinum- containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. If MDS and/or AML are confirmed while on treatment with Lynparza, it is recommended that the patient be treated appropriately. If additional anticancer therapy is recommended, Lynparza should be discontinued and not given in combination with other anticancer therapy.

Pneumonitis
Pneumonitis has been reported in a small number of patients receiving olaparib, and some reports have been fatal. The reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or a radiological abnormality occurs, Lynparza treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, Lynparza treatment should be discontinued and the patient treated appropriately.

Embryofoetal toxicity
Based on its mechanism of action (PARP inhibition), olaparib could cause foetal harm when administered to a pregnant woman. Nonclinical studies in rats have shown that olaparib causes adverse effects on embryofoetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 400 mg twice daily.

Pregnancy/contraception
Lynparza should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 1 month after receiving the last dose of Lynparza (see section 4.6).

Interactions
Olaparib co-administration with strong CYP3A inducers or inhibitors should be avoided (see section 4.5).

In the event that a patient already receiving olaparib requires treatment with a CYP3A inhibitor or P-gp inhibitor, careful monitoring of olaparib associated adverse events and management of those events via the dose reduction strategy is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed.

Pharmacodynamic interactions
Clinical studies of olaparib in combination with other anticancer medicinal products, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity. The recommended Lynparza monotherapy dose is not suitable for combination with other anticancer medicinal products.

Combination of olaparib with vaccines or immunosuppressant agents has not been studied. Therefore, caution should be taken if these drugs are co-administered with olaparib and patients should be closely monitored.

Pharmacokinetic interactions
Effect of other drugs on olaparib
CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. Clinical studies to evaluate the impact of known CYP3A inhibitors and inducers have not been conducted and it is therefore recommended that known strong inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or inducers (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) of these isozymes should be avoided with olaparib (see section 4.4).

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

Effect of olaparib on other drugs
Olaparib may inhibit CYP3A4 *in vitro* and it cannot be excluded that olaparib may increase the exposures to substrates of this enzyme *in vivo*. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (e.g. simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine).

The potential for olaparib to induce CYP3A, CYP1A2, CYP2B6, CYP2C9, CYP2C19 and P-gp is unknown and it cannot be excluded that olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib (see also sections 4.4 and 4.6).

In vitro olaparib may be an inhibitor of P-gp and is an inhibitor of BRCP, OATP1B1, OCT1 and OCT2. It cannot be excluded that olaparib may increase the exposure to substrates of P-gp (e.g. statins, digoxin, dabigatran, colchicine), BRCP (e.g. methotrexate, rosuvastatin and sulfasalazine), OATP1B1 (e.g. bosentan, glibenclamide, repaglinide, statins, and valsartan), OCT1 (e.g. metformin) and OCT2

(e.g. serum creatinine). In particular, caution should be exercised if olaparib is administered in combination with any statin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females
Women of childbearing potential should not become pregnant while on Lynparza and not be pregnant at the beginning of treatment. A pregnancy test should be performed on all pre-menopausal women prior to treatment. Women of childbearing potential must use effective contraception during therapy and for 1 month after receiving the last dose of Lynparza. Due to the potential interaction of olaparib with hormonal contraception an additional non-hormonal contraceptive method and regular pregnancy tests should be considered during treatment (see section 4.5).

Pregnancy
Studies in animals have shown reproductive toxicity including serious teratogenic effects and effects on embryofoetal survival in the rat at maternal systemic exposures lower than those in humans at therapeutic doses (see section 5.3). There are no data from the use of olaparib in pregnant women, however, based on the mode of action of olaparib,Lynparza should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 1 month after receiving the last dose of Lynparza. (See previous paragraph: “Women of childbearing potential/contraception in females” for further information about birth control and pregnancy testing

Breast-feeding
There are no animal studies on the excretion of olaparib in breast milk. It is unknown whether olaparib/or its metabolites are excreted in human milk. Lynparza is contraindicated during breast-feeding and for 1 month after receiving the last dose, given the pharmacologic property of the product (see section 4.3).

Fertility
There are no clinical data on fertility. In animal studies, no effect on conception was observed but there are adverse effects on embryofoetal survival (see section 5.3).

4.7 Effects on ability to drive and use machines

During treatment with Lynparza, asthenia, fatigue, and dizziness have been reported and those patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile
Olaparib monotherapy has been associated with adverse reactions generally of mild or moderate severity (CTCAE 1 or 2) and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving olaparib monotherapy (≥ 10%) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, anaemia, neutropaenia, lymphopaenia, mean corpuscular volume elevation, and increase in creatinine.

Tabulated list of adverse reactions
The following adverse reactions have been identified in clinical studies with patients receiving Lynparza monotherapy. Their frequency is presented using CIOMS III frequency classification and then listed by MedDRA System Organ Class (SOC) and at the preferred term level. Frequencies of occurrence of undesirable effects are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000). This section includes only data derived from completed studies where patient exposure is known.

Table 1 Tabulated list of adverse reactions

	Adverse Reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Metabolism and nutrition disorders	**Very common** Decreased appetite	**Uncommon** Decreased appetite
Nervous system disorders	**Very common** Headache, Dizziness, Dysgeusia,	**Uncommon** Dizziness, Headache
Gastrointestinal disorders	**Very common** Nausea, Vomiting, Diarrhoea, Dyspepsia **Common** Upper abdominal pain, Stomatitis	**Common** Nausea, Vomiting, Diarrhoea **Uncommon** Upper abdominal pain, Stomatitis
General disorders and administration site conditions	**Very common** Fatigue (including asthenia)	**Common** Fatigue (including asthenia)
Investigations	**Very common** Anaemia (decrease in haemoglobin)[a, b], Neutropaenia (decrease in absolute neutrophil count) [a, b], Lymphopaenia (decrease in lymphocytes) [a, b], Increase in blood creatinine [a, d], Mean corpuscular volume elevation [a, c] **Common** Thrombocytopaenia (decrease in platelets) [a, b]	**Very common** Anaemia (decrease in haemoglobin)[a, b], Lymphopaenia (decrease in lymphocytes) [a, b] **Common** Neutropaenia (decrease in absolute neutrophil count) [a, b], Thrombocytopaenia (decrease in platelets) [a, b] **Uncommon** Increase in blood creatinine [a, d]

[a] Represents the incidence of laboratory findings, not of reported adverse events.

[b] Decreases were CTCAE grade 2 or greater for haemoglobin, absolute neutrophils, platelets and lymphocytes.

[c] Elevation in mean corpuscular volume from baseline to above the ULN (upper limit of normal). Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

[d] Data from a double blind placebo controlled study showed a median increase (in percentage change from baseline) up to 23% remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae. 90% of patients were CTCAE grade 0 at baseline, and 10% were CTCAE grade 1 at baseline.

Description of selected adverse reactions
Gastrointestinal toxicities are frequently reported with olaparib therapy and are generally low grade (CTCAE grade 1 or 2) and intermittent and can be managed by dose interruption, dose reduction and/or concomitant medicinal products (e.g. antiemetic therapy). Antiemetic prophylaxis is not required.

Anaemia and other haematological toxicities are generally low grade (CTCAE grade 1 or 2) however, there are reports of CTCAE grade 3 and higher events. Baseline testing, followed by monthly monitoring of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment which may require dose interruption or reduction and/or further treatment.

Paediatric population
No studies have been conducted in paediatric patients.

Other special populations
Limited safety data are available in elderly (age ≥ 75 years) and non-Caucasian patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment in the event of Lynparza overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, ATC code: not yet assigned

Mechanism of action and pharmacodynamic effects
Lynparza is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3), and has been shown to inhibit the growth of selected tumour cell lines *in vitro* and tumour growth *in vivo* either as a standalone treatment or in combination with established chemotherapies.

PARP are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When Lynparza is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this leads to DNA double strand breaks (DSBs) when replication forks meet the PARP-DNA adduct. In normal cells, homologous recombination repair (HRR), which requires functional *BRCA*1 and 2 genes, is effective at repairing these DNA double-strand breaks. In the absence of functional *BRCA*1 or 2, DNA DSBs cannot be repaired via HRR. Instead, alternative and error-prone pathways are activated, such as the non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells have a high DNA damage load relative to normal cells.

In *BRCA*-deficient *in vivo* models, olaparib given after platinum treatment resulted in a delay in tumour progression and an increase in overall survival compared to platinum treatment alone.

Detection of *BRCA* mutation
Patients are eligible for Lynparza treatment if they have a confirmed deleterious or suspected deleterious *BRCA* mutation (i.e., a mutation that disrupts normal gene function) in either the germline or the tumour (detected using an appropriately validated test).

Clinical efficacy
The safety and efficacy of olaparib as a maintenance therapy in the treatment of platinum-sensitive relapsed (PSR) high grade serous ovarian, including fallopian tube or primary peritoneal cancer patients, following treatment with two or more platinum containing regimens, was studied in a Phase II randomised, double blind, placebo controlled trial (study 19). The study compared the efficacy of olaparib maintenance treatment taken to progression with no maintenance treatment in 265 (136 olaparib and 129 placebo) PSR serous ovarian cancer patients who were in response (CR [complete response] or PR [partial response]) confirmed as per RECIST and/or as per CA-125 criteria as defined by Gynecologic Cancer InterGroup (GCIG) (at least a 50% reduction in CA-125 levels from the last pre-treatment sample, confirmed 28 days later) following completion of two or more previous platinum containing chemotherapy. The primary endpoint was PFS (progression-free survival) based on investigator assessment using RECIST 1.0. Secondary efficacy endpoints included OS (overall survival), DCR (disease control rate) defined as confirmed CR/PR + SD (stable disease), HRQoL (health related quality of life), and disease related symptoms. Exploratory analyses of time to first subsequent therapy or death (TFST) and time to second subsequent therapy or death (TSST- an approximation of PFS2) were also performed.

Only PSR patients with partially platinum-sensitive disease (platinum-free interval of 6 to 12 months) and patients with platinum-sensitive disease (platinum-free interval of > 12 months) who were in response following completion of last platinum based chemotherapy were enrolled. Patients could not have received prior olaparib or other PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomisation. Retreatment with olaparib was not permitted following progression on olaparib.

Patients were randomised into the study a median of 40 days after completing their final platinum chemotherapy. They received an average of 3 previous chemotherapy regimens (range 2-11) and 2.6 previous platinum-containing chemotherapies (range 2-8).

Patients in the olaparib group continued to receive treatment longer than those in the placebo group. A total of 54 (39.7%) patients received treatment for > 12 months in the olaparib group compared with 14 (10.9%) patients in the placebo group.

The study met its primary objective of statistically significantly improved PFS for olaparib maintenance monotherapy compared with placebo in the overall population (HR 0.35; 95% CI 0.25-0.49; p<0.00001), moreover, pre-planned subgroup analysis by BRCA-mutation status identified patients with *BRCA*-mutated ovarian cancer (n=136, 51.3%) as the subgroup that derived the greatest clinical benefit from olaparib maintenance monotherapy.

In *BRCA*-mutated patients (n=136) there was a statistically significant improvement in PFS, TFST, and TSST. The median PFS improvement was 6.9 months over placebo for olaparib treated patients (HR 0.18; 95% CI 0.10-0.31; p<0.00001; median 11.2 months versus 4.3 months). The investigator assessment of PFS was consistent with a blinded independent central radiological review of PFS. The time from randomisation to start of first subsequent therapy or death (TFST) was 9.4 months longer for olaparib treated patients (HR 0.33; 95% CI 0.22–0.50; p<0.00001; median 15.6 months versus 6.2 months). The time from randomisation to start of second subsequent therapy or death (TSST) was 8.6 months longer for olaparib treated patients (HR 0.44; 95% CI 0.29-0.67; p=0.00013; median 23.8 months versus 15.2 months. There was no statistically significant difference in OS (HR 0.73;

95% CI 0.45-1.17; p=0.19; median 34.9 months versus 31.9 months). Within the *BRCA*-mutated population the disease control rate at 24 weeks was 57% and 24% for patients in the olaparib and placebo groups, respectively.

No statistically significant differences were observed between olaparib and placebo in patient reported symptoms or HRQoL as measured by improvement and worsening rates in the FACT/NCCN Ovarian Symptom Index (FOSI), Trial Outcome Index (TOI) and Functional Analysis of Cancer Therapy–Ovarian total score (FACT-O total).

The key efficacy findings from Study 19 for *BRCA*-mutated patients are presented in Table 2, and Figures 1 and 2.

Table 2: Summary of key efficacy findings for patients with *BRCA*-mutated PSR ovarian cancer in Study 19

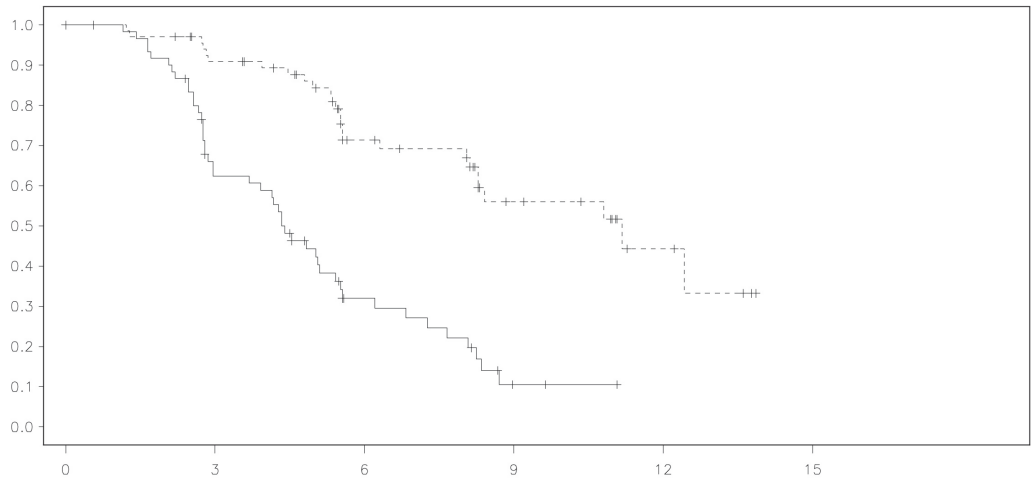
PFS	**N (events/patients) (%)**	**Median PFS (months)**	**HR[a]**	**95% CI**	**p-value**
Olaparib 400 mg bd	26/74 (35%)	11.2	0.18	0.10-0.31	<0.00001
Placebo	46/62 (74%)	4.3			
TSST- an approximation of PFS2	**N**	**Median TSST (months)**	**HR[a]**	**95% CI**	**p-value**
Olaparib 400 mg bd	42/74 (57%)	23.8	0.44	0.29-0.67	0.00013
Placebo	49/62 (79%)	15.2			
Interim OS (52% maturity)	**N**	**Median OS (months)**	**HR[a]**	**95% CI**	**p-value**
Olaparib 400 mg bd	37/74 (50%)	34.9	0.73	0.45-1.17	0.19
Placebo [b]	34/62 (55%)	31.9			

[a] HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model with factors for treatment, time to disease progression on prior penultimate platinum therapy, objective response to prior last platinum therapy and Jewish descent.

[b] Approximately a quarter of placebo treated patients in the *BRCA*-mutated subgroup (14/62; 22.6%) received a subsequent PARP inhibitor.

[N] Number of events/number of randomised patients; OS Overall survival; PFS Progression-free survival; CI Confidence interval; TSST Time from randomisation to start of second subsequent therapy or death.

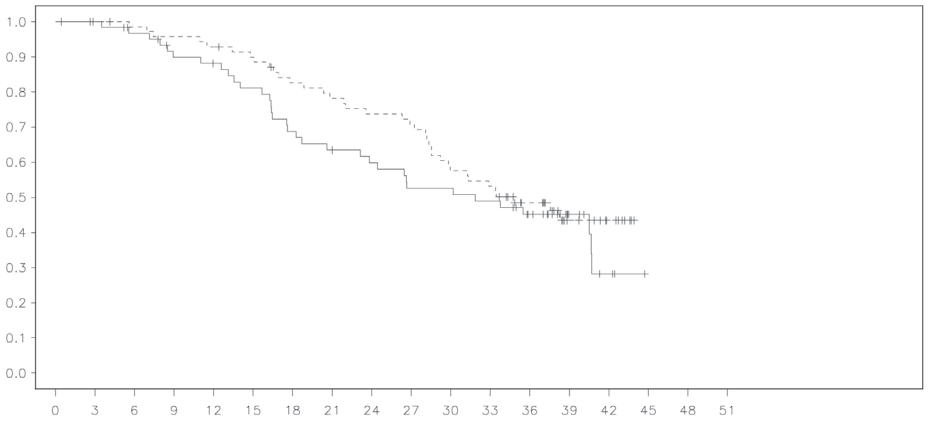
Figure 1 Study 19: Kaplan-Meier plot of PFS in BRCA-mutated patients (53% maturity-investigator assessment)



months	0	3	6	9	12	15
n-olaparib	74	59	34	15	5	0
n-placebo	62	35	13	2	0	0

-----olaparib 400 mg bd twice daily, ____placebo, x-axis=time from randomisation in months, y-axis=PFS (progression-free survival), n-olaparib= number of patients at risk-olaparib, n-placebo=number of patients at risk-placebo

Figure 2 Study 19: Kaplan-Meier plot of OS in *BRCA*-mutated patients (52% maturity)



months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
n-olaparib	74	71	69	67	65	62	56	53	50	48	39	36	26	12	7	0	0	0
n-placebo	62	62	58	52	50	46	39	36	33	29	29	27	21	10	4	0	0	0

-----olaparib 400 mg bd twice daily, ____placebo, x-axis=time from randomisation in months, y-axis=OS (overall survival), n-olaparib= number of patients at risk-olaparib, n-placebo=number of patients at risk-placebo

In Study 19, 18 patients were identified with a somatic tumour *BRCA* mutation (a mutation in the tumour but wildtype in the germline). The limited data for these somatic tumour *BRCA* (*sBRCA*) mutated patients show that fewer patients on olaparib reported progression events or death events compared with placebo (Table 3).

Table 3 Summary of progression-free survival and overall survival: s*BRCA* mutated population in Study 19

	N events/patients (%)
PFS	
Olaparib 400 mg bd	3/8 (38%)
Placebo	6/10 (60%)
OS	
Olaparib 400 mg bd	4/8 (50%)
Placebo	6/10 (60%)

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Lynparza in all subsets of the paediatric population, in ovarian carcinoma (excluding rhabdomyosarcoma and germ cell tumours) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of olaparib at the 400 mg twice daily capsule dose are characterised by an apparent plasma clearance of ~8.6 L/h, an apparent volume of distribution of ~167 L and a terminal half-life of 11.9 hours.

Absorption
Following oral administration of olaparib via the capsule formulation, absorption is rapid with peak plasma concentrations typically achieved between 1 to 3 hours after dosing. On multiple dosing there is no marked accumulation, with steady state exposures achieved within ~3 to 4 days.

Co-administration with food slowed the rate (t_{max} delayed by 2 hours) and marginally increased the extent of absorption of olaparib (AUC increased by approximately 20%). Therefore, it is recommended that patients take Lynparza at least one hour after food, and refrain from eating preferably for up to 2 hours afterwards (see section 4.2).

Distribution
The *in vitro* protein binding of olaparib at plasma concentrations achieved following dosing at 400 mg twice daily is ~82%.

Biotransformation
In vitro, CYP3A4 was shown to be the enzyme primarily responsible for the metabolism of olaparib.

Following oral dosing of ^{14}C-olaparib to female patients, unchanged olaparib accounted for the majority of the circulating radioactivity in plasma (70%) and was the major component found in both urine and faeces (15% and 6% of the dose respectively). The metabolism of olaparib is extensive. The majority of the metabolism was attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulphate conjugation. Up to 20, 37 and 20 metabolites were detected in plasma, urine and faeces respectively, the majority of them representing < 1% of the dosed material. A ring-opened hydroxycyclopropyl moiety, and two mono-oxygenated metabolites (each~10%) were the major circulating components, with one of the mono-oxygenated metabolites also being the major metabolite in the excreta (6% and 5% of the urinary and faecal radioactivity respectively).

In vitro, olaparib produced little/no inhibition of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1 and is not expected to be a clinically significant time dependent inhibitor of any of the P450 enzymes. *In vitro* data also show that olaparib is not a substrate for OATP1B1, OATP1B3, OCT1, BCRP or MRP2 substrate and not an inhibitor of OATP1B3, OAT1 or MRP2.

Elimination
Following a single dose of ^{14}C-olaparib, ~86% of the dosed radioactivity was recovered within a 7 day collection period, ~44% via the urine and ~42% via the faeces. Majority of the material was excreted as metabolites.

Special populations
Renal impairment
The effect of renal impairment on exposure to olaparib has not been studied. Olaparib can be administered in patients with mild renal impairment (creatinine clearance > 50 ml/min). There is limited data in patients with moderate impairment (creatinine clearance < 50 ml/min) or severe impairment (creatinine clearance < 30 ml/min) (see section 4.2).

Hepatic impairment
The effect of hepatic impairment on exposure to olaparib has not been studied. Olaparib is not recommended for use in patients with hepatic impairment (serum bilirubin > 1.5 time upper limit of normal).

Elderly
There are limited data in patients aged 75 and over. A population analysis of the available data has found no relationship between olaparib plasma concentrations and patient age.

Weight
There are no data in obese (BMI > 30 kg/m^2) or underweight (BMI < 18 kg/m^2) patients. A population analysis of the available data has found no evidence that patient weight affects olaparib plasma concentrations.

Race
There are insufficient data to evaluate the potential effect of race on olaparib pharmacokinetics as clinical experience is predominantly in Caucasians (94% of patients included in the population analysis were Caucasian). In the limited data available, there was no evidence of a marked ethnic difference in the PK of olaparib between Japanese and Caucasian patients.

Paediatric population
No studies have been conducted to investigate the pharmacokinetics of olaparib in paediatric patients.

5.3 Preclinical safety data

Genotoxicity
Olaparib showed no mutagenic potential, but was clastogenic in mammalian cells *in vitro*. When dosed orally to rats, olaparib induced micronuclei in bone marrow. This clastogenicity is consistent with the known pharmacology of olaparib and indicates potential for genotoxicity in man.

Repeat dose toxicity
In repeat-dose toxicity studies of up to 6 months duration in rats and dogs, daily oral doses of olaparib were well-tolerated. The major primary target organ for toxicity in both species was the bone marrow, with associated changes in peripheral haematology parameters. These findings occurred at exposures below those seen clinically and were largely reversible within 4 weeks of cessation of dosing. *Ex vivo* studies using human bone marrow cells also confirmed that olaparib is cytotoxic to human bone marrow cells.

Reproductive toxicology
In a female fertility study where rats were dosed until implantation, although extended oestrus was observed in some animals, mating performance and pregnancy rate was not affected. However, there was a slight reduction in embryofoetal survival.

In rat embryofoetal development studies, and at dose levels that did not induce significant maternal toxicity, olaparib caused reduced embryofoetal survival, reduced foetal weight and foetal developmental abnormalities, including major eye malformations (e.g. anophthalmia, micropthalmia), vertebral/rib malformation, and visceral and skeletal abnormalities.

Carcinogenicity
Carcinogenicity studies have not been conducted with olaparib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Lauroyl macrogol-32 glycerides

Capsule shell
Hypromellose
Titanium dioxide (E171)
Gellan gum (E418)
Potassium acetate

Printing ink
Shellac
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

HDPE plastic bottle with a child-resistant closure containing 112 hard capsules.
Pack of 448 capsules (4 bottles of 112 capsules).

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/959/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

AstraZeneca UK Limited
SILK ROAD BUSINESS PARK, MACCLESFIELD, CHESHIRE, SK10 2NA, United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
PAES: In order to further define the long term efficacy of olaparib in patients with platinum sensitive relapsed BRCA mutated high grade serous ovarian cancer, the MAH should submit the final Overall Survival (OS) analysis of study D0810C00019, a phase II randomised, double blind, multicentre study. The clinical study report should be submitted by:	June 2017
PAES: In order to further confirm the efficacy of olaparib in patients with platinum sensitive relapsed BRCA mutated high grade serous ovarian cancer, the MAH should submit the results of study D0816C00002, a phase III randomised double-blind placebo-controlled multicentre study. The clinical study report should be submitted by:	December 2018
PAES: In order to further define the efficacy of olaparib in patients with platinum sensitive relapsed somatic BRCA mutated high grade serous ovarian cancer, the MAH should conduct and submit the results of a phase IV, open label, single arm, non-randomised, multicentre study in patients with relapsed platinum sensitive ovarian cancer who are in complete or partial response following platinum based chemotherapy and who carry loss of function germline or somatic BRCA mutation(s). The clinical study report should be submitted by:	September 2018

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 50 mg hard capsules
olaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg of olaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule.
448 capsules (4 bottles of 112 capsules).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/959/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

lynparza 50 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE/LABEL

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 50 mg hard capsules
olaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg of olaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule.
112 capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/959/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lynparza 50 mg hard capsules
Olaparib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lynparza is and what it is used for

What Lynparza is and how it works

Lynparza hard capsules contain the active substance olaparib. Olaparib is a type of cancer medicine called a PARP (poly [adenosine diphosphate-ribose] polymerase) inhibitor.
In patients with mutations (changes) in certain genes called *BRCA* (breast cancer gene), who are at risk of developing some forms of cancer, PARP inhibitors are able to trigger the death of cancer cells by blocking an enzyme that helps repair DNA.

What Lynparza is used for

Lynparza is used for the treatment of a type of ovarian cancer called "*BRCA*-mutated ovarian cancer". It is used after the cancer has responded to previous treatment with standard platinum-based chemotherapy. A test is used to determine whether you have *BRCA*-mutated cancer.

2. What you need to know before you take Lynparza

Do not take Lynparza:
- if you are allergic to olaparib or any of the other ingredients of this medicine (listed in section 6).

Do not take Lynparza if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist, or nurse before taking Lynparza.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before or during treatment with Lynparza:

- If you have low blood-cell counts on testing. These may be low red blood-cell count (anaemia), low white blood-cell count (neutropaenia), or low blood-platelet count (thrombocytopenia). See section 4 for more information about these side effects. This includes the signs and symptoms you need to look out for (fever or infection, bruising or bleeding). Rarely, these may be a sign of more serious problem with the bone marrow such as 'myelodysplastic syndrome' (MDS) or 'acute myeloid leukaemia' (AML). Your doctor may want to test your bone marrow to check for these problems.

- If you experience any new or worsening symptoms of shortness of breath, coughing, or wheezing. A small number of patients treated with Lynparza reported inflammation of the lungs (pneumonitis). Pneumonitis is a serious condition that can often require hospital treatment.

If any of the above applies to you (or you are not sure), talk to your doctor, pharmacist or nurse.

Tests and checks
Your doctor will check your blood before and during treatment with Lynparza.

You will have a blood test:
- before treatment
- every month for the first year of treatment
- at regular intervals decided by your doctor after the first year of treatment.

If your blood count falls to a low level, it may be necessary to have a blood transfusion (where you are given new blood or blood-based products from a donor).

Other medicines and Lynparza
Tell your doctor, pharmacist, or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines. This is because Lynparza can affect the way some other medicines work. Also some other medicines can affect the way Lynparza works.

Do not take Lynparza if you are taking any other anticancer medicines. Tell your doctor, pharmacist, or nurse if you are planning on receiving a vaccine or a medicine that suppresses the immune system, as you may need to be closely monitored.

Tell your doctor or pharmacist if you are taking any of the following medicines:
- itraconazole - used for fungal infections
- telithromycin, clarithromycin - used for bacterial infections
- boosted protease inhibitors, nelfinavir, indinavir, saquinavir, boceprevir, telaprevir, nevirapine- used for viral infections, including HIV
- rifampicin, rifapentine, rifabutin - used for bacterial infections, including tuberculosis (TB)
- phenytoin, carbamazepine, phenobarbital - used as a sedative or to treat fits (seizures) and epilepsy
- St John's Wort (*Hypericum perforatum*) - a herbal medicine used mainly for depression

Pregnancy and breast-feeding
- You should not take Lynparza if you are pregnant or might become pregnant. This is because it may harm an unborn baby.
- You should avoid becoming pregnant while taking this medicine. You should use effective methods of contraception while taking this medicine and for 1 month after receiving the last dose of Lynparza. It is not known whether Lynparza may affect the effectiveness of some oral

contraceptives. Please tell your doctor if you are taking an oral contraceptive, as your doctor may recommend the addition of a non-hormonal contraceptive method.
- You should have a pregnancy test before starting Lynparza and at regular times during treatment and 1 month after receiving the last dose of Lynparza. If you become pregnant during this time, you must talk to your doctor straight away.
- It is not known whether Lynparza passes into breast milk. Do not breast-feed if you are taking Lynparza and for one month after receiving the last dose of Lynparza. If you are planning to breast-feed, tell your doctor.

Driving and using machines
Lynparza may influence your ability to drive and use machines. If you feel dizzy, weak, or tired while taking Lynparza, do not drive or use tools or machines.

3. How to take Lynparza

Always take this medicine exactly as your doctor, pharmacist, or nurse has told you. Check with your doctor, pharmacist, or nurse if you are not sure.

How much to take
- The recommended dose is 8 capsules (400 mg) taken by mouth twice a day (a total of 16 capsules each day). It is important that you take the total recommended daily dose and continue to do so as instructed by your doctor, pharmacist, or nurse.

How to take
- Take one dose (8 capsules) of Lynparza by mouth with water, once in the morning and once in the evening.
- Take Lynparza at least one hour after eating food. Do not eat preferably for up to 2 hours after taking Lynparza.

If you experience side effects, your doctor may tell you to take Lynparza at a lower dose.

If you take more Lynparza than you should
If you take more Lynparza than your normal dose, contact your doctor or nearest hospital right away.

If you forget to take Lynparza
If you forget to take Lynparza, take your next normal dose at its scheduled time. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. It is important that you are aware of what these side effects may be.

Your doctor may also prescribe other medicines to help control your side effects.

Tell your doctor straight away if you notice any of the following side effects – you may need urgent medical treatment:

Very common (may affect more than 1 in 10 people):
- fever or infection – these may be signs of a low white blood cell count (neutropaenia or lymphopaenia).

- being short of breath, feeling very tired, having pale skin, or fast heart beat - these may be signs of a low red blood cell count (anaemia).

Common (may affect up to 1 in 10 people):
- bruising or bleeding for longer than usual if you hurt yourself - these may be signs of a low blood platelet count (thrombocytopenia).

Tell your doctor straight away if you notice any of the side effects listed above.

Other side effects include:

Very common
- headache
- feeling dizzy
- loss of appetite
- feeling tired or weak
- feeling sick (nausea)
- being sick (vomiting)
- changes in the way food tastes
- indigestion or heartburn (dyspepsia)
- diarrhoea . If it gets severe, tell your doctor straight away
- increase in blood creatinine levels seen from a laboratory test showing how well your kidneys are working
- blood test showing increase of red blood cell size.

Common
- sore mouth (stomatitis)
- pain in the stomach area under the ribs.

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. Your doctor may prescribe a medicine to treat your symptoms such as nausea, vomiting, diarrhoea, and dyspepsia.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lynparza

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the bottle after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Lynparza contains

The active substance is olaparib. Each hard capsule contains 50 mg of olaparib.

The other ingredients (excipients) are:
- Capsule content: lauroyl macrogol-32 glycerides.
- Capsule shell: hypromellose, titanium dioxide (E171), gellan gum (E418), potassium acetate.
- Printing ink: shellac, iron oxide black (E172).

What Lynparza looks like and contents of the pack

Lynparza is a white, opaque, hard capsule, marked with "OLAPARIB 50 mg" and the AstraZeneca logo in black ink.

Lynparza is provided in HDPE plastic bottles containing 112 hard capsules. One pack contains 448 capsules (4 bottles of 112 capsules).

Marketing Authorisation Holder

AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer

AstraZeneca UK Limited
Silk Road Business Park
Macclesfield, Cheshire, SK10 2NA
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Clinical Study Protocol Appendix H	
Drug Substance	Olaparib
Study Code	D0816C00012
Edition Number	2
Date	01 September 2015

Appendix H
Patient Reported Outcomes - FACT-O, ORZORA QoL Additional Items Questionnaire, FACIT Fatigue Scale and Functional Living Index Emesis (FLIE)

FACT-O (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-O (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-O (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
O1	I have swelling in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
O3	I have cramps in my stomach area	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4

ORZORA QoL Additional Items Questionnaire

Please indicate which of the below you may have had issues with by circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	I feel ill with low energy	0	1	2	3	4
	I am able to enjoy life and I am still interested in my hobbies and interests	0	1	2	3	4
	I am satisfied that my family understands my disease	0	1	2	3	4
	I feel I am able to meet the needs of my family	0	1	2	3	4
	I understand the need to take my medication and my treatment regimen	0	1	2	3	4
	My treatment has had significantly negative effects on my QoL	0	1	2	3	4
	I feel like a normal woman	0	1	2	3	4

What are the 3 most significant issues you are struggling with, please list them starting with your worst first?

1.

2.

3.

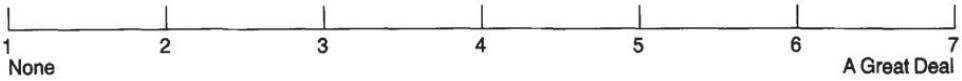
FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

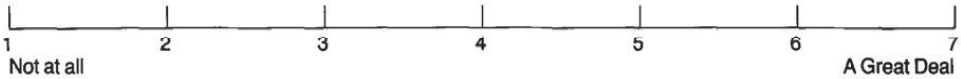
		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 1: Functional living index emesis

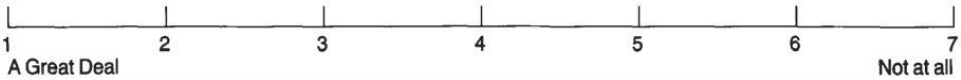
1. How much nausea have you had in the past 3 days?



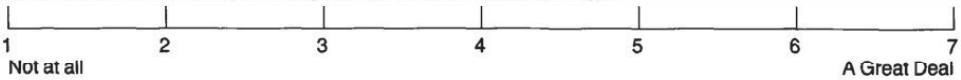
2. Has nausea affected your ability to maintain usual recreation or leisure activities in the past 3 days?



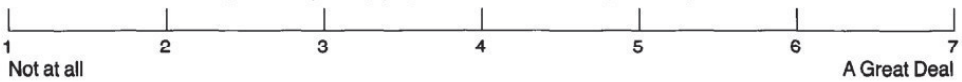
3. Has nausea affected your ability to make a meal or do minor household repairs during the past 3 days?



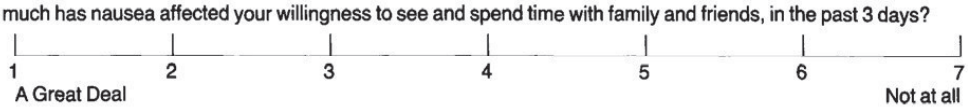
4. How much has nausea affected your ability to enjoy a meal in the past 3 days?



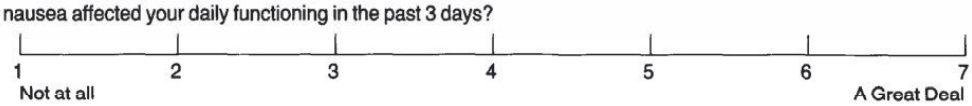
5. How much has nausea affected your ability to enjoy liquid refreshment in the past 3 days?



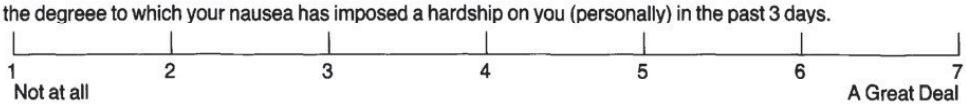
6. How much has nausea affected your willingness to see and spend time with family and friends, in the past 3 days?



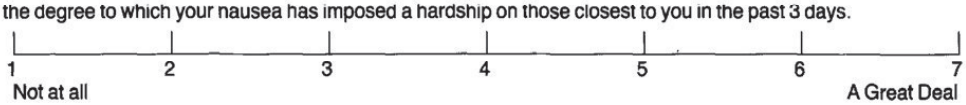
7. Has nausea affected your daily functioning in the past 3 days?



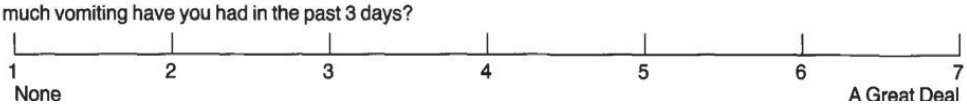
8. Rate the degreee to which your nausea has imposed a hardship on you (personally) in the past 3 days.



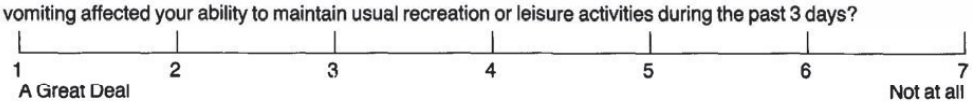
9. Rate the degree to which your nausea has imposed a hardship on those closest to you in the past 3 days.



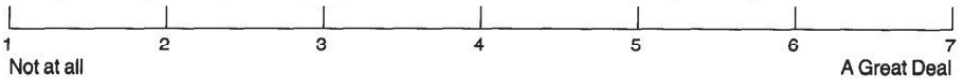
10. How much vomiting have you had in the past 3 days?



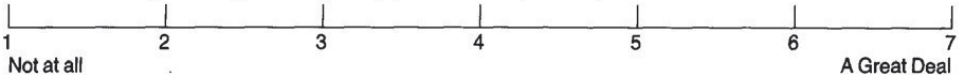
11. Has vomiting affected your ability to maintain usual recreation or leisure activities during the past 3 days?



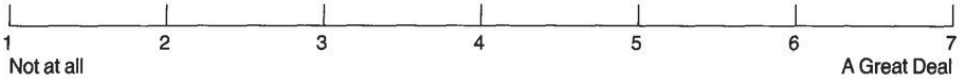
12. Has vomiting affected your ability to complete your usual household tasks during the past 3 days?



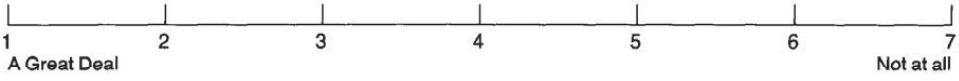
13. How much has vomiting affected your ability to enjoy a meal in the past 3 days?



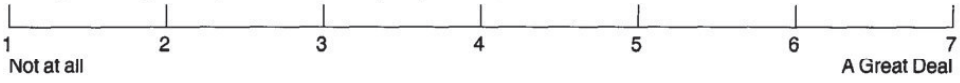
14. How much has vomiting affected your ability to enjoy liquid refreshment in the past 3 days?



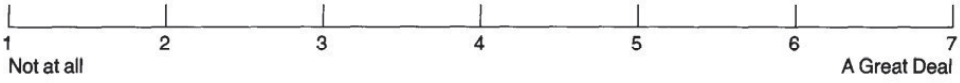
15. How much has vomiting affected your willingness to see and spend time with friends, in the past 3 days?



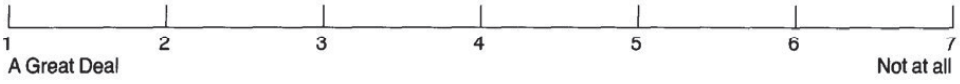
16. Has vomiting affected your daily functioning during the past 3 days?



17. Rate the degree to which your vomiting has imposed a hardship on you (personally) in the past 3 days.



18. Rate the degree to which your vomiting has imposed a hardship on those closest to you in the past 3 days.



Clinical Study Protocol Errata List

Drug Substance	Olaparib
Study Code	D0816C00012
Edition Number	3
Date	15 November 2016

An Open Label, Single Arm, Multicentre Study to Assess the Clinical Effectiveness and Safety of Lynparza (Olaparib) Capsules Maintenance Monotherapy in Platinum Sensitive Relapsed somatic or germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy (ORZORA)

Sponsor: *AstraZeneca AB, 151 85 Södertälje, Sweden.*

Section/Document	Page	Reads	Should read
Section 4 Table 2 last row	47-48-49	Optional tumour sample on progression [j]	Optional tumour sample on progression [k]
Section 4 Table 2 last footnote	47-48-49	h Optional and subject to specific informed consent.	k Optional and subject to specific informed consent.