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Clinical Study Protocol	
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A Phase III, Open Label, Randomised, Controlled, Multi-centre Study to assess the efficacy and safety of Olaparib Monotherapy versus Physician's Choice Single Agent Chemotherapy in the Treatment of Platinum Sensitive Relapsed Ovarian Cancer in Patients carrying germline *BRCA1/2* Mutations

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

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VERSION HISTORY

Version 4.0, 29 September 2017

Rationale for the change: PARP inhibitors now being available as part of clinical practice create significant recruitment challenge for SOLO3 trial. Therefore, recruitment will close once a minimum of 250 patients are randomized instead of 411 as initially planned.

The primary endpoint is objective response rate (ORR). This protocol assumes a response rate of 25% on the chemotherapy arm and a response rate of at least 45% on the Olaparib arm for subjects with measurable disease at baseline according to BICR. The data cut-off for the primary analysis will occur in January 2019 or at a minimum of 6 months after LSI, whichever is sooner, to ensure sufficient patient follow-up to characterize duration of response (DoR) and satisfy a regulatory commitment. The study will retain >80% power to detect a statistically significant difference in ORR at the two-sided 5% level.

The following changes were incorporated into version 4.0 of the protocol:

- Primary objective and endpoint changed from PFS to ORR
- Number of randomized patients changed from 411 to 250
- The data cut-off for the primary analysis will occur in January 2019 or at a minimum of 6 months after LSI, whichever is sooner.
- Figure 1 was updated to reflect current number of patients
- Section 1.1.4 updated based on IB v 14.0 section 6.2
- Section 3.3 added wording regarding randomization timelines after screening closure
- Section 3.10 death was added as criterion for withdrawal
- Figure 2 study flow chart was updated
- Based on IB v 14.0 regular pregnancy testing was added
- Sections 5.4.1 and 10.4.3 were updated regarding PK sample analysis
- Section 6.7 dose reduction scheme was corrected to be in line with section 6.8
- Section 9.2 dispensation of IP was updated
- Section 9.7.1.1 updated based on IB v 14 new data

- Section 10 and page 12 "statistical methods" were updated to reflect changes in number of randomized patients and analyses based on new primary objective and endpoint
- Section 11.4 change of AZ Drug Dictionary to WHODRUG
- Spelling mistake corrected "Friedlander"

Version 3.0, 03 August 2016

The following changes were incorporated into version 3.0 of the protocol:

- Modification made to comments 'a' and 'b' to Table 2.
- Removal of footnote "a" from Tumour assessment visits every 8 or 12 weeks in the header of Table 2
- Addition of "or 12 weeks" to "Subsequent on treatment visits every 4 weeks" in the header of Table 2
- Changes to Sections 6.8.1 and 6.8.2 to align with the current guidelines for haematological toxicity management

Version 2.0, 27 June 2016

The following changes were incorporated into version 2.0 of the protocol:

- Note that when Version 2.0 of the protocol was prepared, the content of the protocol and appendices were incorporated into the new AstraZeneca protocol template resulting in modifications of cover page (tracking version history), removal of Appendix A (signatures) and changes to Appendix numbering.
- Minor editorial changes of a typographical nature were made throughout the protocol for consistency and clarity. Several references to sections were updated for accuracy.
- Changes made to inclusion criteria 3, 6, 7 and 8 in order to allow *BRCA* mutation testing to be carried out during second platinum line.
- Rewording of inclusion criterion 12 for clarity.

- Update regarding new AZ randomization system in Section 3.5.
- Changes to Section 3.8.1 Contraception and Appendix D to align with AstraZeneca's acceptable birth control methods for clinical trial purposes.
- Removal of 'death' from list of situations for IP discontinuation in Section 3.9 and from criteria for withdrawal and discontinuation in Section 3.10.
- Modification made to comments 'f' and 'g' to Table 1.
- Change in Discontinuation of Study Treatment visit window in Table 2 as it should not be performed at -7 days before the subject discontinues IP.
- Visit window of ±3 days added to Visit 2 in Table 2.
- Alignment of tumour assessment visits to the on treatment visits added in comment "b" to Table 2.
- Clarification added to conditions for BP measurement in Section 5.2.4.1.
- Clarification added to PRO information collection process in Section 5.3.1.5.
- Window of ± 5 min added to PK sampling time of 1h post dose at Day 1 (Visit 2) in Table 5 and Section 5.4.2 as well as in comment 'g' to Table 2.
- Information added on data collected in CRF for BRCA testing in Section 5.6.1.1.
- Clarification added to the collection of samples for BRCA testing in Section 5.6.2.
- Clarification added to sample storage and destruction in Section 5.7.2.
- Modification made to Section 6.4 describing SAE reporting process when WBDC is not available.
- Comments added regarding operational aspect of comparator drug supply in Section 9.1.
- Information has been added regarding the effects of other drugs on olaparib and the effects of olaparib on other drugs, to align the information in the protocol with the updated olaparib Investigator's Brochure dated 29 June 2015 (Sections affected: exclusion criterion 11, Section 9.7.1.1 Olaparib drug-drug interactions).
- Updated Section 9.7.1.5 regarding the start of corticosteroids to ensure consistency with exclusion criterion 14.

- Change in source of definition for data validation in Data Management Section 11.4.

Edition number 1, 20 October 2014
Initial creation

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

A Phase III, Open Label, Randomised, Controlled, Multi-centre Study to assess the efficacy and safety of Olaparib Monotherapy versus Physician's Choice Single Agent Chemotherapy in the Treatment of Platinum Sensitive Relapsed Ovarian Cancer in Patients carrying germline *BRCA1/2* Mutations

International Co-ordinating Investigator

Study site(s) and number of patients planned

The study will be conducted in approximately 15 countries worldwide. Approximately 100 centres will be initiated to randomise at least 250 patients. Additional sites may be added dependent on recruitment rates.

Study period		**Phase of development**
Estimated date of first patient enrolled	Q4 2014	III
Estimated date of last patient enrolled	Q2 2018	III

Study design

This open label, randomised, controlled, multi-centre study will assess the efficacy and safety of single agent olaparib vs. standard of care, based on physician's choice of single agent chemotherapy (i.e weekly paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine) in relapsed ovarian cancer patients who have received at least 2 prior lines of platinum based chemotherapy, who have progressed at least 6 months after their last platinum based chemotherapy and who carry a germline deleterious or suspected deleterious *BRCA* mutation. Non-platinum based chemotherapy in this setting can be given to prolong the platinum free interval and can be followed by further platinum treatment at a later relapse or can be considered for patients who are not warranted for further platinum treatment. Due to different routes and schedules of administration of the study treatments and different toxicity profiles, the study is not feasible to be blinded. Given the open label design of the study, rigorous methodology will be employed to ensure robustness of the primary endpoint assessment with a primary analysis of objective response rate (ORR) based on blinded independent central review (BICR) of all patient scans using RECIST 1.1 criteria. Secondary

endpoints will include progression free survival (PFS) by BICR using RECIST 1.1 criteria; time from randomisation to second progression (PFS2); overall survival (OS); CA-125 response; safety assessments and health related quality of life. Full details provided below.

A minimum of 250 patients will be randomised 2:1 (olaparib: chemotherapy) into the trial. The treatment groups include olaparib 300 mg po twice daily tablet continuously, or physician's choice of chemotherapy. The investigator must declare prior to randomisation their choice of chemotherapy i.e. weekly paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine.

The randomisation scheme will be stratified based on:

- Selected chemotherapy (weekly paclitaxel vs. topotecan vs. pegylated liposomal doxorubicin vs. gemcitabine)
- Received prior chemotherapy regimens for ovarian cancer (2 or 3 prior lines of chemotherapy vs. 4 or more)
- Time to disease progression after the end of the last platinum based chemotherapy (6-12 mo vs. > 12 mo)

Objectives

Primary Objective:	**Outcome Measure:**
To determine the efficacy of olaparib vs. physician's choice single agent chemotherapy by assessment of Objective Response Rate (ORR) using blinded independent central review (BICR)	*Objective Response Rate (ORR) by BICR using RECIST 1.1 criteria*

Secondary Objective:	**Outcome Measure:**
To compare the efficacy of single agent olaparib versus physician's choice single agent chemotherapy	• Progression Free Survival (PFS) by BICR using RECIST 1.1 criteria • Time from randomisation to second progression (PFS2) by investigator assessment of radiological, clinical or CA-125 progression • Overall survival (OS) • Time to earliest progression by RECIST 1.1 or CA-125 or death • Time from randomisation to first subsequent therapy or death (TFST) • Time from randomisation to second subsequent therapy or death (TSST)

Secondary Objective:	**Outcome Measure:**
	• Time from randomisation to study treatment discontinuation or death (TDT) • Duration of response (DoR) by BICR using RECIST 1.1 criteria for evaluable patients • Time to response (TTR) by BICR using RECIST 1.1 criteria for evaluable patients
To compare the efficacy of single agent olaparib versus physician's choice single agent chemotherapy on the Health-related Quality of Life (HRQoL) as measured by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O)	• Mean change from baseline in TOI score • Proportion improved (in the absence of subsequent cancer therapy) in TOI score
To assess efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the BRCA genes using variants identified with current and future BRCA mutation assays (e.g. gene sequencing and large rearrangement analysis)	• ORR (by BICR), PFS (by BICR), PFS2, OS, TDT, TFST and TSST, analyses will be performed in those patients whose gBRCAm status is confirmed by the central Myriad test (only required if populations differ from the MDAS (for ORR) or FAS (for PFS) populations) • Development and delivery of a BRCA mutation companion diagnostic
To determine exposure to olaparib following dosing at the 300 mg bd tablet dose and explore exposure-response relationships	

Safety Objective:	**Outcome Measure:**
To assess the safety and tolerability of single agent olaparib vs. physician's choice single agent chemotherapy	Adverse Events (AE), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology

Exploratory Objective:	**Outcome Measure:**
To assess the effect on patient self-reported feelings about side-effects of single agent olaparib versus physician's choice of single agent chemotherapy using the 'Feelings about side-effects' domain of the Cancer Therapy Satisfaction Questionnaire (CTSQ-16)	• Treatment satisfaction score (as measured by the Satisfaction with Therapy scale of the CTSQ-16) • Patient-reported feelings measured by the 'feelings about side-effects' domain of the Cancer Therapy Satisfaction Questionnaire (CTSQ-16)

Exploratory Objective:	**Outcome Measure:**
To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility	• Number, type and reason of hospitalisations and hospital attendances, procedures undertaken and hospital length of stay • Health state utility derived from the HRQL instrument, the EuroQoL EQ5D-5L
To explore methods of estimating overall survival (OS) adjusting for the impact of the control arm receiving subsequent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerise (PARP) inhibitors or imbalances between the treatment arms for other potentially active agents	• Overall survival adjusted for impact of subsequent PARP inhibitors (or other potentially active investigational agents (if appropriate, to support reimbursement appraisals)
To determine the frequency of and describe the nature of BRCA mutation/s in tumour samples and to compare this with germline BRCA mutation status	• BRCA1 and/or BRCA2 mutation status in tumour
To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood samples – archival tumour (mandatory), blood samples at baseline and on disease progression (mandated) and serial biopsies at baseline and disease progression (optional) Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (mandatory), blood samples at baseline and on disease progression (mandated) and serial biopsies at baseline and disease progression (optional) To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (i.e. distribution, safety, tolerability and efficacy) to study treatments and/or susceptibility to disease (optional)	• Potential retrospective tissue biomarker research

The exploratory analyses may not be reported in the clinical study report (CSR). If not, they will be reported separately.

Target patient population

All patients randomised in the study will be selected based on the following 3 principles:

Genetic selection: Documented germline mutation in *BRCA1* or *BRCA2* gene that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Patients with *BRCA*1 and/or *BRCA*2 mutations that are considered to be non-detrimental (eg, "Variants of uncertain clinical significance" or "Variant of unknown significance" or "Variant, favor polymorphism" or "benign polymorphism," etc) will not be eligible for the study. *BRCA* status which is known, for patients determined by a local test will be accepted, however a confirmatory Myriad *gBRCA* test post randomisation will still be required. Genetic counselling should be arranged as per local requirements.

Treatment setting: All patients should have relapsed high grade epithelial ovarian cancer (serous or endometrioid), primary peritoneal or fallopian-tube cancer and should have received at least 2 prior platinum based lines of chemotherapy for ovarian cancer. Patients should be suitable for treatment of relapsed disease with single agent chemotherapy based on physician's choice of weekly paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine. Patients should not have been previously exposed to the selected chemotherapy as a single agent.

Platinum sensitivity: Patients can be either partially platinum sensitive (defined as progression 6 -12 months after the end of the last platinum based chemotherapy) or platinum sensitive (defined as progression >12 months after the end of the last platinum based chemotherapy). Patients who have platinum resistant or refractory disease will not be eligible for the study.

Patients known to have a germline *BRCA* deleterious or suspected deleterious mutation (*gBRCAm*) (i.e. blood) prior to randomisation can enter the study based on this result. The result must be made available to AstraZeneca. In addition the patients must consent to provide 2 blood samples. One sample will be used for a confirmatory *gBRCA* test post randomisation using the current commercial Myriad Integrated BRAC*Analysis* test (gene sequencing and large rearrangement analysis). The second is required for a bridging study to develop and validate the *BRCA* companion diagnostic test for olaparib.

Patients with unknown *BRCA* status must consent to provide 2 blood samples for germline *BRCA* testing by Myriad and comply with all local ethical procedures for such genetic testing. One sample will be used to test for *BRCA* mutations using the current commercial Myriad Integrated BRAC*A*nalysis test prior to study entry. When the result from the Myriad test indicates the patient does have a deleterious or suspected deleterious *BRCA* mutation, the patient can be randomised into the study (providing they have fulfilled all other screening requirements). The second blood sample is required for a bridging study to develop and validate the *BRCA* companion diagnostic test for olaparib. These samples will be required for the study even if the patients are found not to have a deleterious or suspected deleterious *BRCA* mutation.

Duration of treatment

Patients will be randomised (using an IVRS/IWRS) in a 2:1 ratio to the treatments as specified below:

- Olaparib tablets orally 300 mg twice daily (given as two 150mg tablets twice daily); total daily dose of 600 mg
- Physician's choice of chemotherapy (weekly paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine)

All patients should continue to receive study treatment until objective radiological disease progression as per RECIST 1.1 as assessed by the investigator or the patient experiences unacceptable toxicity or they meet any other discontinuation criteria.

All patients should have RECIST assessments until documented evidence of objective radiological progression in accordance with RECIST 1.1, irrespective of treatment decisions (i.e. RECIST follow up until progression even if a patient discontinues study treatment prior to progression and/or receives a subsequent therapy prior to progression). Patients who are determined to have progressed according to RECIST 1.1 criteria by the investigator will have one final RECIST assessment at the next scheduled RECIST visit in order to minimise bias in the BICR assessment in the event the investigator declares objective progression earlier than the BICR. After the primary ORR analysis, central review of scans will no longer be required and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review.

RECIST assessments will be scheduled every 8 weeks (+/- 1 week) from randomisation for 48 weeks and every 12 weeks (+/- 1 week) thereafter. All CT/MRI scans will be sent to an AstraZeneca appointed Clinical Research Organisation (CRO) for blinded independent central review. All treatment decision will be based on investigator's assessment of the scans. Once patients have been discontinued from study treatment, the investigator will be at liberty to define further the most appropriate anti-cancer treatment. Information on all subsequent anticancer treatments will be collected in the eCRF. Within this study, patients on chemotherapy will not be provided olaparib post discontinuation of study treatment.

Following objective disease progression, patients may be allowed to continue study treatment if the investigator believes that the patient continues to receive benefit, the patient is not experiencing serious toxicity and there is no available better alternative treatment that could benefit the patient.

Investigational product, dosage and mode of administration

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib to the investigator as film-coated tablets.

Patients will be administered olaparib tablets orally twice daily (bd) at a dose of 300 mg. Two (2) x 150 mg olaparib tablets should be taken at the same times each morning and evening of each day, approximately 12 hours apart with approximately 240 mL of water.

The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Dose reductions will be managed with 100 mg tablets.

Comparator, dosage and mode of administration

Investigators will declare prior to randomisation in the IVRS their choice of one of the following regimens for each patient:

- Weekly paclitaxel 80 mg/m2 iv on day 1, 8, 15, 22 every 4 weeks
- Pegylated liposomal doxorubicin (PLD) 50 mg/m2 iv day 1 every 4 weeks
- Topotecan 4 mg/m2 iv on day 1, 8, 15 every 4 weeks
- Gemcitabine 1000 mg/m2 iv on day 1, 8, 15 every 4 weeks

Investigators should administer all the chemotherapies as per standard practice guidelines. Within this study there is no provision for patients on the control arm to receive olaparib post discontinuation of their study treatment.

Statistical methods

A minimum of 250 patients will be randomised (2:1 ratio of olaparib:chemotherapy) and the data cut-off for the primary analysis will occur in January 2019 or at a minimum of 6 months after the last subject is randomised whichever is sooner. This is to ensure sufficient patient follow-up to characterize duration of response (DoR) and satisfy a regulatory committment.

With at least 223 subjects, the study will have >80% power to show a statistically significant difference in ORR at the two-sided 5% level, assuming a response rate of 25% on the chemotherapy arm and a response rate of at least 45% on the olaparib arm for subjects with measurable disease at baseline according to BICR. It is anticipated that approximately 90% of subjects will have measurable disease at baseline according to BICR and therefore to ensure adequate power, the sample size will have at least 250 subjects.

The statistical analysis of the efficacy of olaparib will include all randomised patients (Full Analysis Set, FAS), except for the primary endpoint, ORR, which will only include patients with Measurable Disease at baseline as confirmed by BICR (Measurable Disease Analysis Set, MDAS). Treatment groups will be compared on the basis of randomised treatment, regardless of the treatment actually received. When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set. This will include all patients who receive at least one dose of randomised treatment (olaparib or chemotherapy). The safety data will be summarised descriptively and will not be formally analysed.

ORR will be analysed using logistic regression adjusted by the stratification factors. If the number of responses in the individual stratum are too small for a meaningful analysis (less than 5 responses per stratum), a pre-specified strategy to account for such a situation, will be applied. Further details will be documented in the Statistical Analysis Plan. The odds ratio (OR) together with its 95% confidence interval (CI) and p-value will be presented (a OR less than 1 will favour olaparib). The primary analysis will be based on a blinded independent central review (BICR) of objective response by RECIST 1.1, however, a sensitivity analysis will be performed using the investigator-recorded assessment.

Subgroup analyses will be conducted to assess consistency of treatment effect across potential or expected prognostic factors. An analysis will not be performed if there are too few events available for a meaningful analysis of a particular subgroup (i.e., if there are less than 20 patients in a subgroup).

An analysis of PFS, PFS2 and OS will be performed at the same time as the primary analysis of ORR. They will be analysed using a log rank test stratified by the stratification factors. The HR together with its 95% confidence interval (CI) and p-value will be presented (a HR less than 1 will favour olaparib).

A hierarchical testing strategy will be employed where ORR is tested first and key secondary endpoints of PFS, PFS2 and OS will then be tested using a multiple testing procedure with a recycling strategy. PFS will only be tested if the null hypothesis (of no difference) for ORR is rejected. PFS2 will only be tested if the null hypothesis (of no difference) is rejected for both ORR and PFS. OS will only be tested if the null hypothesis (of no difference) is rejected for ORR, PFS and PFS2.

An additional PFS2 and OS analysis will only be conducted with further follow up (~60% OS events) if both ORR and PFS are statistically significant based on the primary analysis and the null hypotheses for PFS2 and/or OS are not rejected at the time of the primary analysis.

Supportive analyses of time to first subsequent therapy (TFST), time to second subsequent therapy (TSST), time to earliest progression by RECIST 1.1 or CA-125 or death and time to discontinuation of study treatment or death (TDT) will be provided, using the same methodology as specified for the analysis of PFS, however no multiple adjustment will be applied as these are viewed as supportive endpoints.

CA-125 response rates and the percentage of patients who had a RECIST response and/or a CA-125 response will be summarised by treatment arm.

The analysis population for HRQoL data will be the FAS. Change from baseline in TOI score will be regarded as the primary analysis of the FACT-O questionnaire and will be analysed using a mixed model for repeated measures (MMRM) analysis of the change from baseline in TOI score for each visit. TOI improvement rate will be based on evaluable QoL data collected from randomisation up to the earliest of starting any subsequent cancer therapy or death. It will be analysed using a logistic regression model using the same covariates as used in the

PFS analyses. Supportive analyses will be performed for the individual TOI domains for both change from baseline score and improvement rates. P-values will not be calculated for these supportive analyses.

Appropriate summaries of exploratory outcome variables and data listings will be produced and compared across the two treatment arms. Graphical methods will be widely used in exploring the characteristics and relationships of outcome variables.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	**Explanation**
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute Myeloid Leukaemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboblastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
Baseline	Refers to the most recent assessment of any variable prior to dosing with study treatment
BICR	Blinded Independent Central Review
Bd	*Bis in die (twice daily)*
BoR	Best Overall RECIST Response
BP	Blood pressure
BRCA	Breast Cancer susceptibility gene
Integrated BRAC*Analysis*	Gene sequencing and large rearrangement analysis
BRCA mutation or *BRCA*m	Breast Cancer susceptibility gene mutation (see *gBRCA* mutation or *gBRCAm*)
CA-125	Cancer Antigen – 125
CDM	Clinical Development Manager
CI	Confidence Interval
Cmax	The maximum or “peak” concentration of a drug observed after its administration
Cmin	The minimum or “trough” concentration of a drug observed after its administration
CR	Complete response
CRF / eCRF	Case Report Form / electronic Case Report Form
CRO	Clinical Research Organisation
CSR	Clinical Study Report

Abbreviation or special term	Explanation
CT	Computed tomography
CTC / CTCAE	Common Terminology Criteria for Adverse Event
CTSQ-16	Cancer Therapy Satisfaction Questionnaire
CYP450	Cytochrome P450 (enzyme)
DCO	Data Cut-Off
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DoR	Duration of response
dUCBT	double Umbilical Cord Blood Transplantation
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
E-code	Enrolment code (allocated by IVRS/IWRS)
ECOG	Eastern Cooperative Oncology Group: A performance status using scales and criteria to assess how a patient's disease is progressing
EQ-5D-5L	EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index
EWB	Emotional well being
FACT-O	Functional Assessment of Cancer Therapy – Ovarian: A multidimensional questionnaire for patients with ovarian cancer
FAS	Full Analysis Set
FFPE	Formalin Fixed Paraffin Embedded
FWB	Functional well being
gBRCA	Germline *BRCA*
gBRCA mutation or *gBRCAm*	The term "*gBRCA* mutation" is used to refer to a germline *BRCA1* or *BRCA2* mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants
gBRCA wt	*gBRCA* wildtype
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyl transferase

Abbreviation or special term	Explanation
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HCT	Haematocrit
HR	Hazard Ratio
HRD	Homologous recombination repair deficiencies
HRQoL	Health-related Quality of Life
IATA	International Air Transport Association
IB	Investigator's brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
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.
INR	International Normalised Ratio
IP	Investigational Product
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LIMS	Laboratory Information Management System
LPLV	Last Patient Last Visit
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MDAS	Measurable disease analysis set
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MRI	Magnetic resonance imaging
MTP	Multiple Testing Procedure
NCI	National Cancer Institute

Abbreviation or special term	Explanation
NE	Not evaluable
OR	Odds ratio
ORR	Objective response rates
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation
PD	Progressive disease
PFS / PFS1	Progression Free Survival
PFS2	Time from randomisation to second progression
PGIC	Patient Global Impression of Change
PI	Principal Investigator
PLD	Pegylated Liposomal Doxorubicin
PK	Pharmacokinetics
p.o.	Per os (by mouth, orally)
PSR	Platinum Sensitive Relapsed
PR	Partial response
PRO	Patient Reported Outcomes
PWB	Physical well being
QoL	Quality of Life
R&D	Research and Development
RBC	Red blood cell
RECIST	Response Evaluation Criteria In Solid Tumours. This study will use RECIST version 1.1
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SSB	Single strand break
SWB	Social well being
Study treatment	Olaparib
TDT	Time from randomisation to study treatment discontinuation or death
TFST	Time from randomisation to first subsequent therapy or death
t_{max}	Time at which maximum or "peak" concentration (C_{max}) of a drug is observed after its administration

Abbreviation or special term	Explanation
TOI	Trial Outcome Index
TSST	Time from randomisation to second subsequent therapy or death
ULN	Upper limit of normal
WBC	White blood cells
WBDC	Web Based Data Capture

1 INTRODUCTION

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). In the United States there were 22,240 new cases and 14,030 deaths estimated in 2013 (Siegel et al 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. Ovarian cancer is diagnosed predominantly in postmenopausal women with the majority of cases being diagnosed in women over 50 years of age. More than 70% of the patients are diagnosed with advanced disease and less than 40% of women with ovarian cancer are cured (Fleming et al 2009, Jemal et al 2010).

The standard therapy for advanced ovarian cancer consists of radical debulking surgery followed by post-operative platinum-based first-line chemotherapy. Although 70% to 80% of patients respond to such initial treatment, the majority subsequently relapse (Ledermann and Kristleit 2010). Once relapsed, disease is no longer considered curable. The progression free interval after the last platinum based chemotherapy has prognostic value. Based on it the GCIG Consensus defined 4 categories of patients: 'platinum sensitive' progressing more than 12 months after the last chemotherapy; 'partially-platinum sensitive' progressing between 6 and 12 months after the last chemotherapy; 'platinum resistant' progressing within 6 months of the last chemotherapy and 'platinum refractory' progressing during or within 4 weeks of the last dose of chemotherapy (Friedlander et al 2011). Most patients with platinum-sensitive disease will respond further to platinum based chemotherapy and many will receive multiple lines of treatment over time but ultimately accumulate toxicities that limit the administration of further platinum or develop platinum resistance. The role of platinum based chemotherapy in 'partially platinum sensitive' patients remains controversial and platinum break with single agent chemotherapy presents another treatment option (Colombo et al 2013). Patients with platinum resistant or refractory disease have generally poor prognosis and treatment options consist of non-platinum monotherapy including weekly paclitaxel, topotecan, pegylated liposomal doxorubicin, gemcitabine (Ledermann et al 2014). Following each subsequent relapse, patients experience progressively shorter progression-free intervals and ultimately succumb to their disease (Colombo et al 2010).

Recently, the European Medicine Agency has approved the use of the angiogenesis inhibitor bevacizumab in combination with platinum based chemotherapy in first line and relapsed setting in platinum sensitive patients and in combination with non-platinum-based chemotherapy in platinum resistant patients, presenting another treatment option. No targeted treatment is currently licensed for ovarian cancer patients with germline *BRCA* mutation (*gBRCAm*).

BRCA mutated ovarian cancer

The *BRCA1* and *BRCA2* genes were identified in the early 1990's as genetic elements underlying inherited breast and ovarian cancer. *BRCA* mutations are particularly prevalent in people of Jewish descent (Roa et al 1996) and often associated with high-grade serous ovarian cancer, where the germline *BRCA1* and *BRCA2* (*gBRCA*) frequency in unselected patients is as high as 17% (Alsop et al 2012a; Alsop et al 2012b) and up to 38% in patients with platinum-sensitive recurrent high-grade serous ovarian cancer (Dann et al 2012). Women inheriting a mutated copy of *BRCA1* or *BRCA2* have a 39% and 11% risk, respectively, of developing ovarian cancer by the age of 70 (Antoniou et al 2003). Germline *BRCA1* mutation confers a higher risk of developing ovarian cancer than germline *BRCA2* mutation (Antoniou et al 2003) and ovarian tumours in *BRCA1* mutation carriers generally arise several years, and in some cases up to a decade, earlier compared with those in *BRCA2* (Alsop et al 2012a). Thus, *BRCA1* mutations are more commonly identified in ovarian cancer patients than *BRCA2* mutations, with mutation frequencies of 62% vs. 38%, respectively (Alsop et al 2012a; Alsop et al 2012b). Deficiency in *BRCA* ultimately leads to the accumulation of genetic alterations as a result of the failure of cells to arrest and repair DNA damage or to undergo apoptosis, resulting in tumorigenesis.

Consistent with this biology, patients with *BRCA* mutations often have platinum-sensitive epithelial ovarian cancer (Dann et al 2012; Hennessy et al 2010), associated with improved PFS outcomes (Tan et al 2008, Hennessy et al 2010). The largest series to date of 1,213 patients with *BRCA* mutations (Bolton et al 2012) demonstrates that *BRCA1*- and *BRCA2*-associated ovarian cancers have a better prognosis compared with sporadic ovarian cancers (Hyman and Spriggs 2012). However, the overall pattern of disease remains similar, with disease recurrence after each line of chemotherapy and patients ultimately dying from their disease.

Patients with *BRCA*-mutated ovarian cancer currently have identical treatment options as sporadic ovarian cancer patients. They 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. Ovarian cancer patients with *BRCA* mutation represent a small, well defined and medically recognised subpopulation for whom despite the potential for personalised healthcare, no targeted treatment currently exists.

1.1.1 PARP inhibition as a target for *BRCA* mutated ovarian cancer

Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB).

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents. PARP inhibition is a novel approach to targeting tumours with deficiencies in DNA repair mechanisms.

Numerous DNA single stranded breaks (SSBs) occur naturally as the result of normal metabolic activities and environmental factors, including UV light and radiation. PARP plays an important role in identifying and repairing SSBs. Olaparib, through direct PARP enzyme inhibition and trapping of PARP with the DNA in an open configuration, prevents repair of SSBs. As cells undergo replication, SSBs are converted to harmful double-strand breaks (DSBs). In normal cells, DSBs are repaired by a DNA repair mechanism called homologous recombination repair. Cells with homologous recombination repair deficiency (HRD), resort to the more error prone repair mechanism called non-homologous end joining (NHEJ). In cells with HRD, DNA damage accumulates and leads to high genomic instability and eventual cell death. Cancer with HRD would thus be more sensitive to induction of cell death by PARP inhibitors.

To date, there is no well-established and available-for-testing single genetic/genomic signature which defines HRD. The most common function-altering mutations associated with HRD are a mutation in the breast cancer susceptibility gene (*BRCA*) *BRCA1* or *BRCA2* genes, which code for two of the critical proteins in homologous recombination repair. *BRCA1* and *BRCA2* mutations that are defined as deleterious and suspected deleterious mutations are associated with loss of function of the protein.

Consistent with the DNA repair biology, individuals with hereditary *gBRCA* mutations have an increased risk of breast, ovarian, pancreatic and other cancers. The cancer cells in such individuals have lost the second normal copy of the *BRCA* gene (loss of the wildtype allele), whereas their normal cells still have one normal allele as well as one mutated allele. Normal cells in patients who carry a *gBRCA* mutation can therefore repair DSBs with the functioning wildtype *BRCA* allele. In cancer cells, the loss of heterozygosity leaves the non-functional *gBRCA* allele as the sole copy. PARP inhibition takes advantage of this difference and preferentially kills the cancer cells with minimal toxicity to normal cells (Rottenberg et al 2008; Hay et al 2009).

Deficiencies in other known homologous recombination repair pathway proteins (eg ATM, RAD51B, RRAD51C, RAD54L, RAD51D, FANCL J/BRIP1, FANCI, FANCL, FANCN (PALB2), BARD1, CHEK1, CHEK2, CDK12 and PPP2R2A1) may confer sensitivity to PARP inhibitors (McCabe et al 2006). However, these occur less commonly than *BRCA* mutations in ovarian cancer (Pennington et al 2014) and currently there is no simple assay to define an 'HRD phenotype'.

HRD increases sensitivity to platinum-based chemotherapy, as the deficiency impairs the ability of cancer cells to repair the direct platinum-induced double strand DNA breaks. Thus, platinum sensitivity is often associated with an HRD tumour type.

1.1.2 Pre-clinical experience

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

1.1.3 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 anaesthetized dog or any behavioural, autonomic or motor effects in the rat at the doses studied.

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

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

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

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

1.1.4 Clinical experience

Clinical experience with olaparib is fully described in the current version of the olaparib IB. The olaparib capsule formulation was registered for use in the EU and US in December 2014. The recommended olaparib monotherapy capsule dose is 400 mg bd. The Phase III registration studies and most new clinical studies are investigating the tablet formulation which delivers the therapeutic dose of olaparib in fewer dose units than the capsule. The recommended olaparib monotherapy tablet dose under investigation is 300 mg bd. As of 15 December 2016, approximately 6558 patients are estimated to have received olaparib in the clinial programme including AstraZeneca-sponsored studies (3923 patients), a MAP (676 patients), ISSs and collaborative group studies (1959 patients). An estimated 4475 patients with ovarian, breast, pancreatic, gastric and a variety of other solid tumours are estimated to have received treatment with olaparib in AstraZeneca-sponsored, interventional studies (3799 patients) and the MAP (676 patients). Since 2012/2013, most new clinical studies have utilised the tablet formulation which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule. Of the 4475 patients, 2109 received the capsule formulation, 2341 received the tablet formulation, and 25 received both capsule and tablet. In the AstraZeneca-sponsored, interventional studies, olaparib was given either as monotherapy (2618 patients) or in combination with chemotherapy or other anti-cancer agents, including studies where patients received monotherapy and combination therapy sequentially (n=1181). Data from the available pre-clinical studies and subsequent clinical development programme demonstrate that olaparib appears to be active and generally well tolerated in patients with solid tumours including those with BRCA mutated cancers. In ovarian cancer, responses have been seen in all patient groups, including platinum resistant and refractory cancer. From the

available data to date in patients with advanced cancer, there is no evidence of any unexpected toxicity following long-term olaparib (capsule) monotherapy exposure.

Adverse laboratory findings and/or clinical diagnoses considered to be associated with administration of olaparib monotherapy include haematological effects (anaemia, neutropenia, lymphopenia, thrombocytopenia, MCV elevation and increase in blood creatinine), nausea and vomiting, decreased appetite, diarrhoea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), headache and dizziness. Most of these events were generally mild or moderate in intensity. In a relatively small number of patients, pneumonitis, MDS/AML and new primary

malignancies have been observed. Evidence from across the development programme for olaparib does not support a conclusion that there is a causal relationship between olaparib and these events. These are important potential risks for olaparib and are being kept under close surveillance.

1.2 **Research hypothesis**

Olaparib, administered as monotherapy improves objective response rates (ORR) compared to physician's choice of single agent standard of care chemotherapy (weekly paclitaxel, topotecan, pegylated liposomal doxorubicin (PLD), or gemcitabine) in patients with relapsed platinum sensitive ovarian cancer who have received at least 2 prior platinum based lines of chemotherapy and carry *gBRCA* mutation.

1.3 **Rationale for study design, doses and control groups**

The proposed phase III trial is designed to confirm the benefit of olaparib by assessing the efficacy and safety of olaparib monotherapy vs. physician's choice of single agent standard of care non-platinum based chemotherapy in patients with *gBRCA* mutated relapsed platinum sensitive ovarian cancer who had received at least 2 prior lines of platinum based chemotherapy. Treatment of platinum sensitive relapse usually involves re-treatment with platinum regimen. However, non-platinum based chemotherapy can be given in this setting to prolong the platinum free interval and can be followed by further platinum treatment at a later relapse or can be considered for patients who are not warranted for further platinum treatment. Weekly paclitaxel, topotecan, PLD and gemcitabine are the most commonly used non platinum agents in relapsed ovarian cancer with no agent proven to be superior to the others. Therefore, physician's choice of chemotherapy is provided for the control arm of the study.

Due to different routes and schedules of administration of the chemotherapies on the control arm as well as their different tolerability profiles, the study is not feasible to be blinded. Given the open label design of the study, rigorous methodology will be employed to ensure robustness of the primary endpoint assessment with a primary analysis of ORR based on blinded independent central review (BICR) of all patients' scans.

A number of secondary endpoints will provide further support for the clinical benefit of olaparib in this patient population including progression free survivial (PFS) by BICR, time

from randomisation to second progression (PFS2), overall survival (OS), CA-125 response, safety assessments and health related quality of life.

1.3.1 Rationale for study treatment dose

The safety and efficacy of olaparib has been demonstrated in the clinical programs using predominantly the capsule formulation (400 mg [8 capsules] twice daily). However, an improved tablet formulation (2 tablets twice daily) has been developed and will be used in this study. The recommended tablet formulation of olaparib as monotherapy is 300 mg twice daily which is considered similar in terms of efficacy and safety to the capsule 400 mg twice daily dose. However, the capsule and the tablet formulations are not bioequivalent, as observed in Study 24 where 300 mg twice daily tablet dose matched or exceeded the exposure of the 400 mg capsule in terms of AUC, C_{maxss}, and C_{minss}. The tolerability profile of the 300 mg bd tablet dose in Study 24 was considered similar to the 400 mg bd capsule formulation. The most common AEs were consistent with the known safety profile of olaparib, namely low grade nausea, vomiting, fatigue, and anaemia. Tablet formulation is used across the olaparib Phase III programme.

Olaparib, when given via the tablet formulation has a t_{max} typically between 0.5 and 2 hours and mean terminal half-life of approximately 12 to 15 hours. Based on the average single dose $t_{½}$, it would be expected that steady state exposure would be achieved within approximately 3 days of commencing dosing with olaparib. It is metabolized primarily by the CYP3A4 enzyme and is excreted through the urine (35% to 50%) and feces (12% to 60%).

Further information is provided in the olaparib Investigator's Brochure.

1.4 Benefit/risk and ethical assessment

1.4.1 Unmet need

Ovarian cancer is a serious, life-threatening disease for which new medicines are needed. The current mainstay of therapy consists of multiple lines of chemotherapy, where a platinum agent is routinely employed. However, despite good initial responses in many platinum sensitive patients, the toxicity burden of platinum agents, including carboplatin is significant, with cumulative toxicity limiting the duration of treatment possible at each line of therapy. There is a large unmet need for a therapy that is well tolerated and can provide an alternative to chemotherapy for a well-defined patient population who have already received at least 2 prior platinum based chemotherapy lines and will be next treated with non-platinum single agent chemotherapy.

PARP inhibitors are the first targeted agents to be used in selected ovarian cancer patients. The biology of PARP predicts for benefit in *BRCAm* patients, regardless of whether their mutation is detected by blood (germline) or tumour testing (Ledermann et al 2014). The selection of patients in this trial will be based on a blood test (the Myriad Integrated BRAC*Analysis*® test) for the detection of germline *BRCA* mutations. Therefore the risk

benefit focuses on findings in the *gBRCAm* subgroup in accordance with the selected study population.

1.4.2 Clinical benefit of olaparib monotherapy in patients with PSR *gBRCA* mutated ovarian cancer

The pooled analysis from 6 olaparib (Phase I and II) monotherapy clinical studies consisting of 300 patients with *gBRCA* mutated relapsed ovarian cancer (including fallopian tube and primary peritoneal), of whom 273 had measurable disease and were evaluable for response, demonstrated response rate with olaparib in the overall group of 36% (97/273) and 7.4 months duration of response. The majority of the patients (n=223) had received 3 or more prior lines of therapy and of these, 205 patients had measurable disease. In these patients the response rate was 31% (64/205) and duration of response was 7.8 months. Nineteen percent (n=51) of the 273 patients with measurable disease were classified as platinum sensitive. The response rate in the platinum sensitive patients was 53% (27/51) and the duration of response was 8.2 months.

The majority of the patients in the pooled analysis (n=193) were enrolled in study 42, a Phase II, open-label, non-randomised, non-comparative, multicentre study to assess the efficacy and safety of olaparib (400 mg capsules) given orally bd in patients with advanced cancers, which were refractory to standard therapy or for whom no suitable, effective/curative therapy existed, and who had a confirmed genetic *BRCA1* and/or *BRCA2* mutation. In Study 42, there were 193 patients with relapsed ovarian cancer (including fallopian tube and primary peritoneal), of whom 167 had measurable disease. In this overall group the response rate was 36% (60/167) and duration of response was 7.4 months (Kaufman et al 2013). Patients were also analysed by their platinum sensitivity status, if their last treatment was platinum based, and in the group of patients who were classed as platinum sensitive but ineligible to receive further platinum, the response rate with olaparib was higher than in the group of patients with platinum resistant disease (60% [15/25] vs. 15% [6/40]) respectively (AZ data on file).

Furthermore, 97 patients in the pooled analysis were included from Study 12, a randomised, open-label phase II dose-finding study of olaparib monotherapy (200 mg bd and 400 mg bd capsule) vs. pegylated liposomal doxorubicin (PLD) in *gBRCAm* ovarian cancer patients who had failed previous platinum therapy and were not considered candidates for further platinum treatment. The primary analysis of PFS (Investigator assessment) comparing both doses of olaparib to PLD did not demonstrate a statistically significant difference (n=81, HR=0.88 95% CI (0.51, 1.56)), median PFS 6.5 months, 8.8 months and 7.1 months for the olaparib 200 mg, olaparib 400 mg and PLD groups (Kaye S et al 2012). Objective response rates were 25%, 31% and 18% for the olaparib 200 mg, 400 mg and PLD groups respectively. However, a pre-specified subgroup analysis in the platinum sensitive patients in the trial (n=48), showed HR for PFS numerically higher for olaparib 400mg group vs. PLD (n=34, HR 0.61 95% CI (0.24,1.50)) with median PFS 9.2 months in the olaparib 400 mg group and 7.4 months in the PLD group and response rates 47% and 26% respectively.

Finally, a recently reported investigator-sponsored, randomised, open label, phase II clinical trial, not included in the pooled analysis, compared olaparib single agent (400mg bd capsule) vs. olaparib (200 mg bd capsule) in combination with cediranib (30 mg daily) in platinum sensitive relapsed ovarian cancer patients who had failed at least one prior chemotherapy (Liu J et al 2014). Fifty two percent of the patients in the trial had known *gBRCA* mutation (47/90) and in this pre-defined subgroup, olaparib single agent showed median PFS of 16.5 months and response rate of 63%. Phase III trials for the combination of olaparib and cediranib are planned to better characterise the efficacy and safety of the combination.

1.4.3 Safety and tolerability of olaparib

The tolerability profile of olaparib is well characterised and suitable for long-term dosing until disease progression in patients with relapsed platinum sensitive ovarian cancer who carry *gBRCAm*. The common AEs of olaparib include nausea, vomiting, fatigue and anemia. The low grade and intermittent nature of these events means that nausea and vomiting can be treated empirically and anti-emetic prophylaxis is not required. Hematological changes including anemia should be monitored routinely using standard assessments of hematological laboratory parameters, as is routine for patients receiving anti-cancer therapies. Where necessary, AEs can be managed by interrupting or reducing the olaparib dose, treating symptomatically with standard procedures (eg, antiemetics for nausea and vomiting, occasional blood transfusions for anemia) or in rare cases by permanently discontinuing olaparib treatment.

Long-term tolerability to olaparib maintenance therapy has been demonstrated, with 45%, 25% and 17% of the patients in the *gBRCA* subgroup in study 19 in the olaparib arm remaining on treatment at 1 year, 2 years and 3 years, respectively. Most patients remained on treatment until disease progression, with only a small number of patients permanently discontinuing study treatment due to AEs (9.4% with olaparib vs. 0% with placebo in the *gBRCA* subgroup). MDS/AML are considered AEs of special interest as they may be related to agents that affect DNA repair, including chemotherapy. These events have been seen in less than 1% of patients who received olaparib. These events will be actively monitored in the ongoing phase III studies, including prompted follow-up.

1.4.4 Myelodysplastic syndrome/acute myeloid leukaemia(t-AML)

Development of secondary myelodysplastic syndrome (MDS)/therapy-related acute myeloid leukemia (t-AML) is an AE of interest, as it may be related to products that affect DNA repair mechanisms. As of 20 August 2014, 21 reports of MDS/AML have been received out of 2,866 olaparib treated patients, giving a cumulative reporting rate of 0.7%. Across the clinical study program, MDS has also been reported for 2 patients who did not receive olaparib: one patient that received placebo in Study 19 (0.8% [1/128]) and one patient treated with pegylated liposomal doxorubicin as the comparator in Study 12 (3.1% [1/32]), giving a similar reporting rate. Of the 21 cases reported across the development program, 14 have been reported in monotherapy studies and 7 in combination studies. Sixteen of the patients had a *gBRCA* mutation. In 13 cases, the diagnosis was MDS without a report of AML. There were 8 cases of AML. The median age of onset was 63 years and all but 3 patients had ovarian

cancer. Eight patients had a history of previous cancer. The mean time from diagnosis of current cancer to onset of MDS or AML was 62 months. All patients had associated history features that may have contributed to the development of MDS/AML. All had received chemotherapy with DNA damaging agents, including platinum, taxanes and anthracyclines. Many patients received multiple treatment regimens over multiple years and 7 patients had also received radiotherapy. Four patients were treated with olaparib for less than 6 months, 5 patients were treated for between 6 months and 1 year, 4 patients were treated for between 1 and 2 years, and 8 patients were treated for more than 2 years. In the majority of cases, MDS occurred while on treatment with olaparib but in 4 cases the onset of MDS was more than 5 months after olaparib was discontinued.

Epidemiological studies from the literature have indicated a higher risk of therapy related AML in ovarian cancer populations, particularly those receiving alkylating agents and pelvic irradiation with a wide range of incidence rates. In two recent studies using the US SEER database, Vey et al identified 98 cases of t-AML among 63,359 epithelial ovarian cancer cases, with an overall incidence of 0.15% (Vay et al 2011), while another SEER-based study in registries representing 9.5% of the US population for years 1975-2008 reported 72 t-AML cases among 23,180 ovarian cancer patients (incidence of 0.31%) (Morton et al 2013). The SEER data need to be reviewed with caution because MDS is not collected in cancer registries as it is considered pre-malignant and the data from the early episodes are confounded by a higher contemporaneous use of Melphalan, which is no longer prescribed. While non-clinical data suggest bone marrow progenitor cell populations are reduced temporarily following olaparib treatment, there is no evidence to date linking olaparib treatment to the generation of abnormal bone marrow precursors. Moreover, preclinical data suggest potential benefit with PARP inhibitors in MDS/AML and clinical trials are now underway to assess this effect (Gaymes et al 2008).

To ensure robust safety monitoring, additional safety measures are incorporated into the phase III protocol: normal hematological values are required before inclusion into the studies; regular blood tests are required while on treatment to detect hematological abnormalities early and in case of prolonged cytopenias patients are to be referred to a hematologist and bone marrow analysis should be considered. If a diagnosis of MDS is confirmed, study treatment must be discontinued and the event, treatment, course and outcome must be reported as an SAE. Furthermore, any cases of MDS/AML will be collected in the long term survival follow up and an Independent Data Monitoring Committee (IDMC) will review the emerging safety data from the trial.

1.4.5 New Primary Malignancies

Similar to MDS/AML, the development of new primary malignancies is an adverse event of interest that may be related to products that affect DNA repair mechanisms, and of relevance to patients with germline *BRCA* mutations, who are at risk of developing other cancers. As of 20 August 2014, 21 of the 2,866 patients who had received olaparib had reported 23 events of a new primary malignancy (other than MDS/AML), giving a cumulative incidence of 0.73% for new primary malignancies. Ten of the events were non-melanoma skin cancers. The

remaining events were: breast cancer (n=3), intraductal proliferative breast lesion, lung cancer (n=2), gastric cancer, plasma cell myeloma, malignant melanoma, precursor T-lymphoblastic lymphoma/leukemia, colon cancer, tongue neoplasm and malignant muscle neoplasm (pre-existing before olaparib treatment). In addition, one patient in the placebo arm of the double blind Study 19 reported a new primary malignancy event of bladder cancer (1/128, [0.78%]). All patients had already previously received various chemotherapy agents including multiple cycles of DNA damaging platinum containing chemotherapies, taxanes, anthracyclines and other alkylating and DNA damaging agents. Four patients were reported to have had prior radiotherapy. Nineteen patients had a documented breast cancer gene mutation (*BRCA 1 or 2*). Seven patients had an earlier diagnosis of a previous cancer (ovarian, cervix, breast, peritoneal) prior to their cancer under investigation in the olaparib study. New primary malignancies are monitored actively in the phase III trial both during study treatment and during the long term survival follow up.

In summary, this trial is designed to confirm the benefit and assess the safety of olaparib monotherapy vs. single agent standard of care non-platinum based chemotherapy in patients with *gBRCA* mutated relapsed platinum sensitive ovarian cancer who have received at least 2 prior platinum based lines of chemotherapy. Based on the results presented above and data from the full clinical program to date, olaparib is considered to have a positive benefit risk profile for the treatment of this small well-defined population. Moreover, another confirmatory phase III study (SOLO2) designed to establish the clinical benefit of olaparib maintenance therapy in relapsed platinum sensitive *BRCA* mutated ovarian cancer patients is ongoing and expected to be fully enrolled with 264 patients in Q1 2015.

1.5 **Study Design**

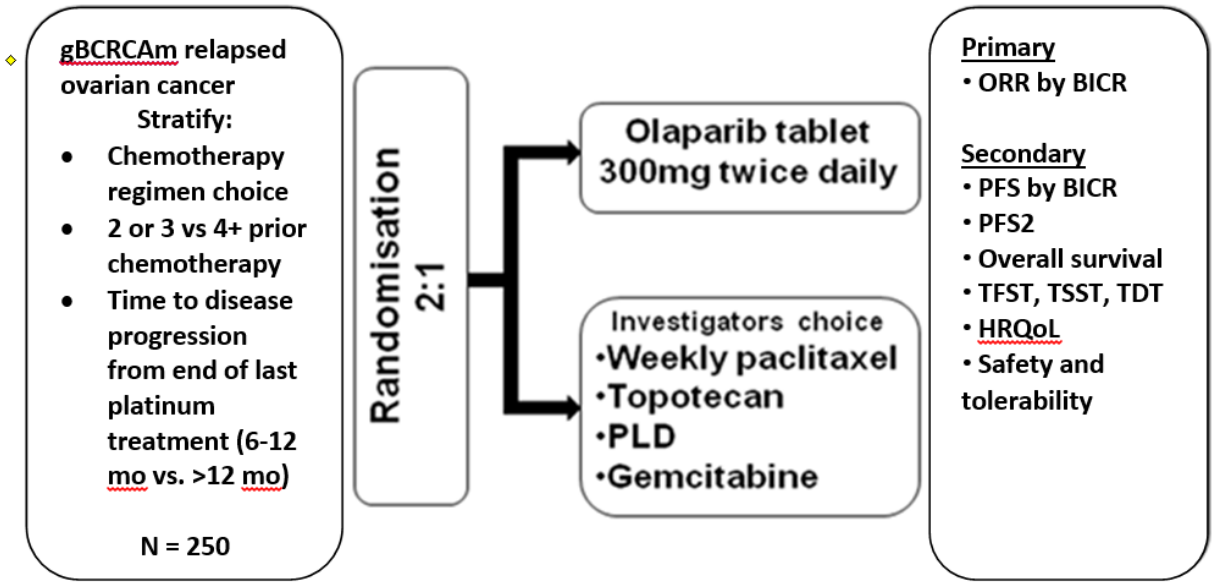
This open label, randomised, controlled, multi-centre study will assess the efficacy and safety of single agent olaparib vs. standard of care, based on physician's choice of single agent chemotherapy (i.e weekly paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine) in relapsed ovarian cancer patients who have received at least 2 prior lines of platinum based chemotherapy, who have progressed at least 6 months after their last platinum based chemotherapy and who carry a germline deleterious or suspected deleterious *BRCA* mutation. Non-platinum based chemotherapy in this setting can be given to prolong the platinum free interval and can be followed by further platinum treatment at a later relapse or can be considered for patients who are not warranted for further platinum treatment. Due to different routes and schedules of administration of the study treatments and different toxicity profiles, the study is not feasible to be blinded. Given the open label design of the study, rigorous methodology will be employed to ensure robustness of the primary endpoint assessment with a primary analysis of ORR based on blinded independent central review (BICR) of all patient scans. Secondary endpoints will include progression free survival (PFS) by BICR; time from randomisation to second progression (PFS2); overall survival (OS); CA-125 response; safety assessments and health related quality of life. Full details provided below.

A minimum of 250 patients will be randomised 2:1 (olaparib: chemotherapy) into the trial. The treatment groups include olaparib 300 mg po twice daily tablet continuously, or physician's choice of chemotherapy. The investigator must declare prior to randomisation their choice of chemotherapy i.e. weekly paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine. The investigator should administer all the chemotherapies as per standard practice guidelines.

The randomisation scheme will be stratified based on:

- Selected chemotherapy (weekly paclitaxel vs. topotecan vs. pegylated liposomal doxorubicin vs. gemcitabine)
- Received prior chemotherapy regimens for ovarian cancer (2 or 3 prior lines of chemotherapy vs. 4 or more)
- Time to disease progression after the end of the last platinum based chemotherapy (6-12 months vs. > 12 months)

Figure 1 Study Diagram



2 STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To determine the efficacy of olaparib vs. physician's choice single agent chemotherapy by assessment of Objective Response Rate (ORR) using blinded independent central review (BICR)	• Objective Response Rate (ORR) by BICR using RECIST 1.1

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure:**
To compare the efficacy of single agent olaparib versus physician's choice single agent chemotherapy	• Progression Free Survival (PFS) by BICR using RECIST 1.1 • Time from randomisation to second progression (PFS2) by investigator assessment of radiological, clinical or CA-125 progression • Overall survival (OS) • Time to earliest progression by RECIST 1.1 or CA-125 or death • Time from randomisation to first subsequent therapy or death (TFST) • Time from randomisation to second subsequent therapy or death (TSST) • Time from randomisation to study treatment discontinuation or death (TDT) • Duration of response (DoR) by BICR using RECIST 1.1 criteria for evaluable patients • Time to response (TTR) by BICR using RECIST 1.1 criteria for evaluable patients
To compare the efficacy of single agent olaparib versus physician's choice single agent chemotherapy on the Health-related Quality of Life (HRQoL) as measured by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O)	• Mean change from baseline in TOI score • Proportion improved (in the absence of subsequent cancer therapy) in TOI score
To assess efficacy of olaparib in patients identified as having a deleterious or	• ORR (by BICR), PFS (by BICR), PFS2, OS, TDT, TFST and TSST, analyses will be

Secondary Objective:	**Outcome Measure:**
suspected deleterious variant in either of the BRCA genes using variants identified with current and future BRCA mutation assays (e.g. gene sequencing and large rearrangement analysis)	performed in those patients whose gBRCAm status is confirmed by the central Myriad test (only required if populations differ from the MDAS (for ORR) or FAS (for PFS) populations) • Development and delivery of a BRCA mutation companion diagnostic
To determine exposure to olaparib following dosing at the 300 mg bd tablet dose and explore exposure-response relationships	

2.3 Safety objectives

Safety Objective:	**Outcome Measure:**
To assess the safety and tolerability of single agent olaparib vs. physician's choice single agent chemotherapy	Adverse Events (AE), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology

2.4 Exploratory objectives

Exploratory Objective:	**Outcome Measure:**
To assess the effect on patient self-reported feelings about side-effects of single agent olaparib versus physician's choice of single agent chemotherapy using the 'Feelings about side-effects' domain of the Cancer Therapy Satisfaction Questionnaire (CTSQ-16)	• Treatment satisfaction score (as measured by the Satisfaction with Therapy scale of the CTSQ-16) • Patient-reported feelings measured by the 'feelings about side-effects' domain of the Cancer Therapy Satisfaction Questionnaire (CTSQ-16)
To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility	• Number, type and reason of hospitalisations and hospital attendances, procedures undertaken and hospital length of stay • Health state utility derived from the HRQL instrument, the EuroQoL EQ5D-5L
To explore methods of estimating overall survival (OS) adjusting for the impact of the control arm receiving subsequent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerise (PARP) inhibitors or imbalances between the treatment arms for other potentially active agents	• Overall survival adjusted for impact of subsequent PARP inhibitors (or other potentially active investigational agents (if appropriate, to support reimbursement appraisals)
To determine the frequency of and describe the nature of BRCA mutation/s in tumour samples and to compare this with germline	• BRCA1 and/or BRCA2 mutation status in tumour

Exploratory Objective:	**Outcome Measure:**
BRCA mutation status	
To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood samples – archival tumour (mandatory), blood samples at baseline and on disease progression (mandated) and serial biopsies at baseline and disease progression (optional) Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (mandatory), blood samples at baseline and on disease progression (mandated) and serial biopsies at baseline and disease progression (optional) To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (i.e. distribution, safety, tolerability and efficacy) to study treatments and/or susceptibility to disease (optional)	• Potential retrospective tissue biomarker research

The exploratory analyses may not be reported in the clinical study report (CSR). If not, they will be reported separately.

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

The patient population should be selected without bias.

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

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

3.1 Inclusion criteria

Patients who already know they have a mutation in the *BRCA1* or *BRCA2* gene that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) must fulfil all of the criteria below. Patients that do not know their

mutation status, and who are being considered for this trial must fulfil all of the criteria marked with an asterisk (*) below prior to *BRCA* mutation testing being carried out. To perform the BRCA testing investigator judgement of patient's potential eligibility to the study should be assessed as per Table 1 and by reviewing the inclusion/exclusion criteria. All inclusion criteria will then be assessed following confirmation that patient carry an appropriate *BRCA* mutation.

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

2. *Patients must be ≥ 18 years of age

3. *Female patients with histologically diagnosed relapsed high grade serous ovarian cancer (including primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer (please refer to Appendix H). Patients are eligible to undergo BRCA testing even if they have not yet had recurrence or progression of disease >6 months (>/=183 days) after completion of their last platinum therapy.

4. Documented germline mutation in BRCA1 and/or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function)

5. At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by CT/MRI and is suitable for repeated assessment

6. Patients must have received at least 2 prior platinum based lines of chemotherapy for ovarian cancer

7. Patients must be partially platinum sensitive (defined as progression 6 -12 months after the end of the last platinum based chemotherapy) or platinum sensitive (defined as progression > 12 months after the end of the last platinum based chemotherapy)

8. Patients must be suitable to start treatment with single agent chemotherapy based on physician's choice of weekly paclitaxel or topotecan or pegylated liposomal doxorubicin (PLD), or gemcitabine

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

    - Haemoglobin ≥ 10.0 g/dL with no packed red cells transfusions in the past 28 days
    - Absolute neutrophil count (ANC) ≥ 1.5 x 109/L
    - Platelet count ≥ 100 x 109/L

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

10. *Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (see Appendix F)

11. *Patients must have a life expectancy ≥ 16 weeks

12. *Patient must show evidence of non-childbearing status: negative urine or serum pregnancy test within 7 days before first study drug dose (for women of childbearing potential) or must be postmenopausal. Postmenopausal is defined as:

    - Age ≥ 60 yrs,
    - Age < 60 and any one of the conditions below:
        - Amenorrheic for 1 year or more in the absence of chemotherapy and/or hormonal treatments;
        - Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) and oestradiol levels in the post menopausal range for women under 60;
        - Radiation-induced oophorectomy with last menses >1 year ago;
        - Chemotherapy-induced menopause with >1 year interval since last menses;
        - Surgical sterilisation (bilateral oophorectomy or hysterectomy)

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

14. *Formalin fixed, paraffin embedded (FFPE) tumour sample from the primary or recurrent cancer **must** be available for central testing. If there is not written confirmation of the availability of an archived tumour sample prior to enrolment the patient is **not** eligible for the study

For inclusion in the optional exploratory genetic research and/or the optional biomarker research, patients must fulfil the relevant criteria below:

- Provision of informed consent for genetic research
- Provision of informed consent for biomarker research

If a patient declines to participate in the optional exploratory genetic research or the optional biomarker research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study.

3.2 Exclusion criteria

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

1. *Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
2. *BRCA* 1 and/or *BRCA*2 mutations that are considered to be non detrimental (e.g., "Variants of uncertain clinical significance" or "Variant of unknown significance" or "Variant, favor polymorphism" or "benign polymorphism" etc.)
3. *Previous randomisation in the present study
4. Exposure to any investigational product within 30 days or 5 half lives (whichever is longer) prior to randomisation
5. *Any previous treatment with a PARP inhibitor, including olaparib
6. *Patients who have platinum resistant or refractory disease defined as progression during or within 6 months of their last platinum based chemotherapy
7. *Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years. Patients with primary triple negative breast cancer may be eligible provided they completed their definitive treatment more than 3 years ago and they remain breast cancer disease free prior to randomization
8. Resting ECG with clinically abnormal findings
9. Patients receiving any systemic chemotherapy within 3 weeks prior to first dose of study treatment (or a longer period depending on the defined characteristics of the agents used) or radiotherapy within 2 weeks prior to first dose of study treatment
10. Previous single agent exposure to the selected chemotherapy regimen (e.g. investigator cannot choose weekly paclitaxel for a patient who has previously received single agent weekly paclitaxel)

11. *Concomitant use of known potent CYP3A4/5 inhibitors such as ketoconazole, itraconazole, boosted protease inhibitors (ritonavir, indinavir, saquinavir, telithromycin, nelfinavir, boceprevir, telaprevir) and clarithromycin

12. *Persistent toxicities (> Common Terminology Criteria for Adverse Event (CTCAE) grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE grade 2 peripheral neuropathy

13. *Patients with myelodysplastic syndrome/treatment related acute myeloid leukaemia (t-AML) or with features suggestive of MDS/AML

14. *Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to randomisation. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days prior to randomisation

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

16. *Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that would limit ability to comply with study procedures, and any other medical condition that in the opinion of the investigator places the patient at unacceptable risk of toxicity

17. *Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication

18. *Breastfeeding women

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

20. *Patients with known active hepatitis B or C or HIV

21. *Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUCBT)

22. *Whole blood transfusions in the last 120 days prior to central *BRCA* testing (packed red blood cells transfusions are acceptable, for timing refer to inclusion criteria no.9)

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomisation

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

The investigator(s) will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed. For patients with unknown *BRCA* status, specific informed consent for *BRCA* testing must be given by the patient prior to any study procedures for the Screening Part 1 visit.

2. Assign potential patient a unique enrolment number, beginning with 'E#' (This number will be obtained through Interactive Voice/Web Response System [IVRS/IWRS]).

3. Determine patient eligibility. See Section 3.

4. Obtain the randomisation code (patient number) through IVRS/IWRS.

If a patient discontinues or withdraws from participation in the study, then her enrolment/randomisation codes cannot be reused.

Screening will be closed when sufficient patients have been enrolled to reach the required number of randomised patients. Any patients who remain in screening at this time will be eligible for randomization up to 2 months after screening is closed. If after 2 months the patient is not yet eligible for randomization, randomization into the study will be closed and these patients will be considered screen failures.

3.4 Procedures for handling incorrectly enrolled or randomised patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the investigator should inform the Study Physician immediately, and a discussion should occur between the Study Physician and the investigator

regarding whether to continue or discontinue the patient from treatment. The Study Physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Eligible patients will be randomised in a 2:1 ratio.

The actual treatment given to individual patients will be determined by a randomisation scheme that has been loaded into the Interactive Voice Response System / Interactive Web Response System (IVRS/IWRS) database. The randomisation scheme will be produced by a computer software program called AZRand (AZ Randomisation system). A blocked randomisation will be generated for all centres.

The randomisation scheme will be stratified based on the following:

- Selected chemotherapy (weekly paclitaxel vs. topotecan vs. pegylated liposomal doxorubicin vs. gemcitabine)
- Received prior chemotherapy regimens for ovarian cancer (2 or 3 prior lines of chemotherapy vs. 4 or more)
- Time to disease progression after the end of the last platinum based chemotherapy (6-12 mo vs. > 12 mo)

Specific information concerning the use of IVRS/IWRS will be provided in separate manual.

It is recommended that patients commence study treatment on the day of randomisation if possible, and if not, then ideally within 3 days.

3.6 Methods for ensuring blinding

Not applicable.

3.7 Methods for unblinding

Not applicable.

3.8 Restrictions

3.8.1 Contraception

Patients and their partners, who are sexually active and of childbearing potential, must agree to the use of TWO highly effective forms of contraception in combination, throughout the period of taking study treatment and for 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse when this is in line with their preferred and usual lifestyle. For details refer to Appendix D Acceptable Birth Control Methods.

3.9 Discontinuation of investigational product

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

- Patient's 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
- Objective progression according to RECIST 1.1 criteria (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 (IP)

By discontinuing from IP, the patient is not withdrawn from 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. If possible, they will be seen and assessed by an investigator(s). 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/Sub-Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. Patients who discontinue treatment prior to documented RECIST progression should continue to be followed for progression as per the protocol schedule. Once progressed, all patients should be followed for PFS2 and OS as per the protocol schedule. In addition, they will record on the eCRF the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation. If patients discontinue study treatment, 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 the study treatment 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 3.10.3). All new AEs and SAEs occurring during the 30 calendar days after the last dose of study treatment must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 6.4) 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 event occurring subsequent to the 30-day follow-up AE

reporting period that the investigator assesses as possibly related to the study medication should also be reported as an AE.

Any patient who has not yet shown objective radiological disease progression at withdrawal from IP should continue to be followed as per RECIST 1.1 as detailed in Table 3.

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

3.10 **Criteria for withdrawal**

Reasons for withdrawal from the study:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment.
- Incorrectly enrolled patients i.e., the patient does not meet the required inclusion/exclusion criteria for the study. This option is only applicable to patients not randomised into the study (ie screen failures identified prior to randomisation).
- Patient lost to follow-up (section 3.10.3).
- Death.

* If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- to further participation in the study including any further follow up (e.g., survival calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples (see Section 5.8.2).

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded in eCRF. This reason for study withdrawal is only valid for screen failures (not randomised patients).

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.

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 patient notes, hospital records, contacting the patient's 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.

3.10.3 Lost to follow-up

Patient is considered lost to follow up when any of the following attempts of contact are failed:

- 3 attempts of either phone calls, faxes or emails
- Having sent 1 registered letter/certified mail
- One unsuccessful effort to check the vital status of the patient using publicly available sources, if allowed by local regulations

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 CRF. 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

Figure 2 Study Flow Chart

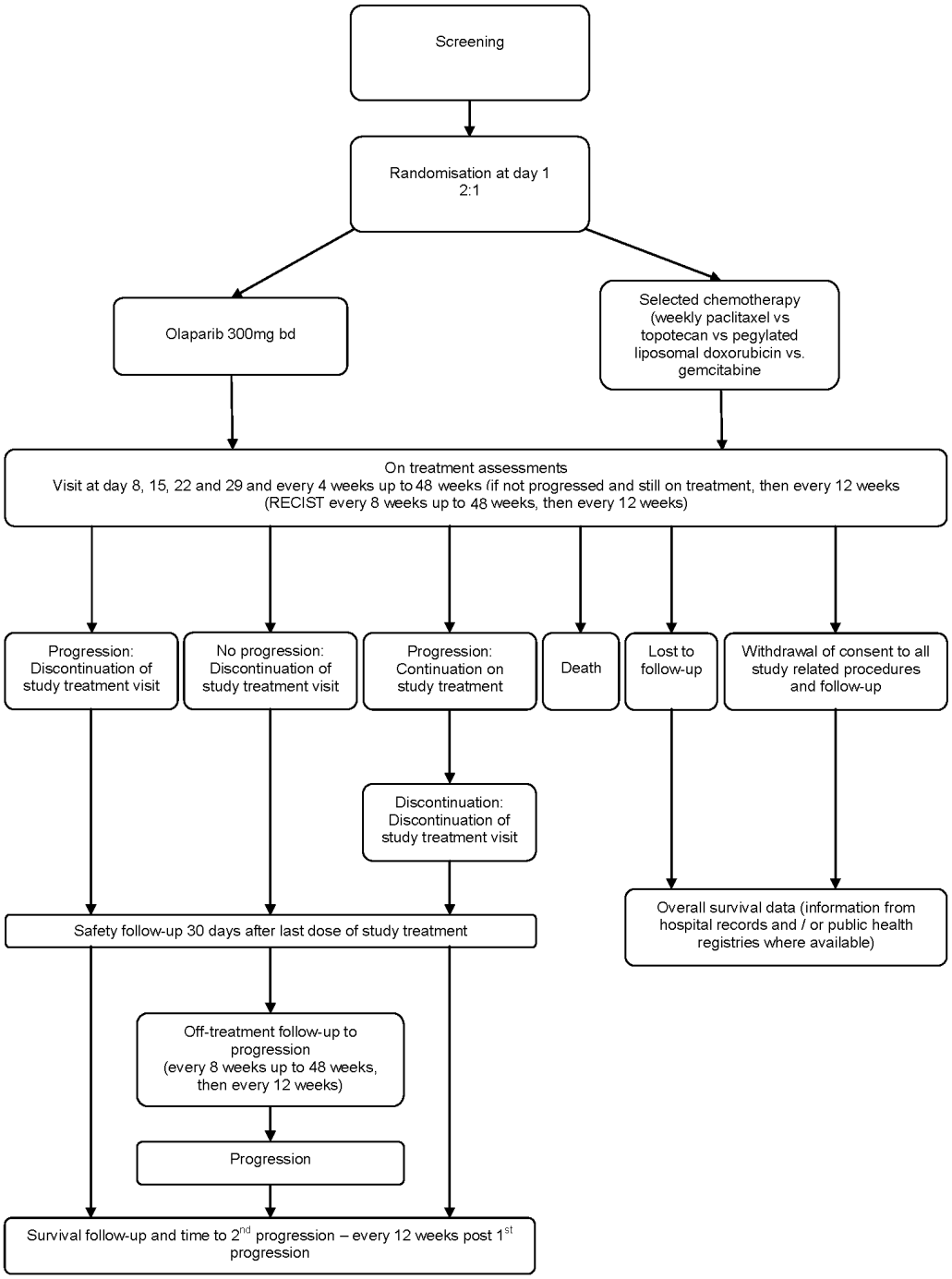

Screening
Randomisation at day 1
2:1
Olaparib 300mg bd
Selected chemotherapy
(weekly paclitaxel vs
topotecan vs pegylated
liposomal doxorubicin vs.
gemcitabine
On treatment assessments
Visit at day 8, 15, 22 and 29 and every 4 weeks up to 48 weeks (if not progressed and still on treatment, then every 12 weeks
(RECIST every 8 weeks up to 48 weeks, then every 12 weeks)
Progression:
Discontinuation of
study treatment visit
No progression:
Discontinuation of
study treatment visit
Progression:
Continuation on
study treatment
Death
Lost to
follow-up
Withdrawal of consent to all
study related procedures
and follow-up
Discontinuation:
Discontinuation of
study treatment visit
Safety follow-up 30 days after last dose of study treatment
Overall survival data (information from
hospital records and / or public health
registries where available)
Off-treatment follow-up to
progression
(every 8 weeks up to 48 weeks,
then every 12 weeks)
Progression
Survival follow-up and time to 2nd progression – every 12 weeks post 1st
progression

Table 1 Study Schedule – Screening

Day	**Part 1** Patient with unknown *gBRCA* status only	**Part 2** Patients with known *gBRCA* mutation	**Part 3** if patient is still eligible after Part 2
Day		**-28 to –1**	**-7 to –1**
Informed consent	X[a]	X[l]	
Demographics	X	X	
Medical and surgical history		X	
Prior cancer therapies including radiotherapy		X	
Inclusion/exclusion criteria	X[b] (all * inclusion/exclusion criteria)	X	
ECOG Performance Status (0-2)		X	
Physical examination		X	
Vital signs, body weight, height (Includes BP, pulse and temperature)		X	
ECG[c]			X
Haematology / clinical chemistry[d]			X
Urinalysis		X	
Pregnancy test[e]			X
Blood sample for disease specific marker (CA-125)		X	
Blood sample for determination of *BRCA* status via Myriad	X[f]	X[g]	
Tumour Assessment (CT or MRI according to RECIST v1.1)[h]		X	
Adverse Events (from time of consent)	X[i]	X	X
Concomitant medications		X	X
Archival tumour sample (mandatory)[j]		X	

Table 1 Study Schedule – Screening

Day	**Part 1** Patient with unknown *gBRCA* status only	**Part 2** Patients with known *gBRCA* mutation	**Part 3** if patient is still eligible after Part 2
Baseline tumour sample (optional)[k]		X	

[a] Informed consent for central Myriad germline BRCA testing.
[b] See section 3 for specific eligibility criteria for having the *gBRCA* status Myriad assessment sample.
[c] ECG should be performed once the patient has been in the supine position for at least 5 minutes in each case.
[d] Coagulation tests will only be required if clinically indicated.
[e] Pre-menopausal women of child-bearing potential must have a negative urine or serum pregnancy test within 7days prior to starting treatment. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.
[f] Patients with an unknown *gBRCA* status must provide a blood sample at Screening Part 1 for Myriad *gBRCA* testing. Any patient who consents to study related Myriad *gBRCA* status testing must also provide a second blood sample taken at the same time for the purpose of developing and validating future diagnostic test(s) for *BRCA* mutations, if allowed by local regulations
[g] Patients with known *gBRCA* status from local lab result must provide a blood sample at Screening Part 2 for confirmatory purposes. Their involvement in the study will not be affected by the result of the Myriad test. Any patient who consents to study related Myriad *gBRCA* status testing must also provide a second blood sample taken at the same time for the purpose of developing and validating future diagnostic test(s) for *BRCA* mutations, if allowed by local regulations.
[h] CT/MRI of the chest, abdomen and pelvis not more than 28 days prior to study treatment start and as close as possible to the start of study treatment.
[i] Only SAE's related to blood sampling for the Myriad *gBRCA* test will be collected at this visit.
[j] Mandatory sample for all randomised patients only. Confirmation required in clinical notes regarding availability of sample during the screening period, however, sample will only be submitted once the patient has been randomised.
[k] The biopsied tumour should not be assessed as a target lesion as part of the RECIST assessments if there are other lesions available. The biopsy should be taken after the baseline scan has been performed.
[l] Informed consent for participation in the main study.

Table 2 Study Schedule – On Study Treatment and Discontinuation

Visit Number	**2**	**3**	**4**	**5**	**6**	**Visit No. 7 onwards** Subsequent on treatment visits every 4 or 12 weeks[a] Tumour assessment visits every 8 or 12 weeks[b]	**Discontinuation of study treatment**	**Safety Follow-up 30 days after last dose of IP**
Day	1	8	15	22	29	Day 1of next visit period (Visit 7 equals day 57 (week 8) then visit 8 equals day 85 (week 12) etc)		
Visit Window	*±3d*	*±3d*	*±3d*	*±3d*	*±3d*	*±3d*	*+7d*	*±7d*
Randomisation	X							
Physical exam[c]	X				X	X	X	
Vital signs, body weight[c] (Includes BP, pulse and temperature) and ECG	As clinically indicated							
ECOG performance status	X					X	X	
Haematology / clinical chemistry[f]	X	X	X	X	X	X	X	X
Pregnancy test n	X				X	X (Pregnancy testing for females of childbearing potential must be conducted at regular intervals (e.g. monthly, but ideally aligned with the on site visit schedule)		
Blood sample for disease specific marker (CA-125)	X				X	X	X	
Blood sample for PK analysis (*Subset of patients*)[g]	X				X			

Table 2 Study Schedule – On Study Treatment and Discontinuation

Visit Number	**2**	**3**	**4**	**5**	**6**	**Visit No. 7 onwards** Subsequent on treatment visits every 4 or 12 weeks[a] Tumour assessment visits every 8 or 12 weeks[b]	**Discontinuation of study treatment**	**Safety Follow-up 30 days after last dose of IP**
Day	1	8	15	22	29	Day 1of next visit period (Visit 7 equals day 57 (week 8) then visit 8 equals day 85 (week 12) etc)		
Visit Window	*±3d*	*±3d*	*±3d*	*±3d*	*±3d*	*±3d*	*+7d*	*±7d*
Tumour Assessment (CT or MRI according to RECIST v1.1)[b]						Every 8 weeks for 48 weeks and every 12 weeks thereafter until PD, one additional RECIST assessment required after PD declared by the investigator		
Adverse Events[h]	X	X	X	X	X	X	X	X
Concomitant medications including blood transfusions	X	X	X	X	X	X	X	X
EQ-5D-5L[i]	X				X	X	X	
FACT-O[i]	X				X	X	X	
CTSQ-16						X (week 24 only)	X	
PGIC						X (week 24 only)	X	
Resource use	X				X	X	X	X
Olaparib dispensed/returned[j]	X				X[i]	X[i]	X	
Subsequent cancer therapy following discontinuation of study treatment [k]								X

Table 2 Study Schedule – On Study Treatment and Discontinuation

Visit Number	**2**	**3**	**4**	**5**	**6**	**Visit No. 7 onwards** Subsequent on treatment visits every 4 or 12 weeks[a] Tumour assessment visits every 8 or 12 weeks[b]	**Discontinuation of study treatment**	**Safety Follow-up 30 days after last dose of IP**
Day	1	8	15	22	29	Day 1of next visit period (Visit 7 equals day 57 (week 8) then visit 8 equals day 85 (week 12) etc)		
Visit Window	*±3d*	*±3d*	*±3d*	*±3d*	*±3d*	*±3d*	*+7d*	*±7d*
Blood sample for pharmacogenetics (optional patient consent required)	X							
Tumour biopsy on progression (optional)[l]							X	
Blood samples for biomarker analysis[m]	X						X	

[a] Visit to take place on Day 1 of a 4 week (28 day) visit period up to 48 weeks (if not progressed and still on treatment), then on day 1 of a 12 week visit period relative to date of randomisation. Visits for patients who remain on treatment post progression should take place every 12 weeks.

[b] Follow-up assessments will be performed every 8 weeks (±1 week) up to 48 weeks, then every 12 weeks (±1 week) relative to date of randomisation. 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 must be followed until RECIST disease progression. 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. Patients who are determined to have progressed according to RECIST 1.1 criteria by the investigator will have one final RECIST assessment at the next scheduled RECIST visit.

[c] Vital signs if clinically indicated during study treatment. Physical examination should be performed according to the schedule, after the baseline assessment it is not necessary to record the details on an eCRF. Any clinically significant changes should be recorded as adverse events.

[d] Temperature and weight only required if clinically indicated.

[e] ECG will only be performed if clinically indicated. ECG should be performed once the patient has been in the supine position for at least 5 minutes in each case.

[f] Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, 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. Safety bloods for the patients randomised to single agent chemotherapy should be performed as per standard practice. All randomised patients will have safety bloods taken weekly during the 1st month on treatment followed by 4 weekly assessments until discontinuation of study treatment. Safety bloods will be taken at the 30-day FU visit as well. CA-125 will be tested at baseline and every month thereafter until serological disease progression as per GCIG CA-125 criteria.

[g] PK sampling to be performed in a subset of patients. Sampling times: Day 1 pre-dose & 1 hour ± 5 min post-dose; Day 29 pre-dose, 0.5-1 hour, 1-3 hours 3-6 hours and 6-12 hours (see section 5.4). NOTE: the post-dose samples are timed from the first dose of the day.

[h] 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.

[i] FACT-O and EQ5D will be collected at baseline, day 29, week 8, 16, 24, 32, 40 and 48 (+/- 1 week) from start of study treatment regardless of treatment discontinuation or disease progression. Patients who have progressed as per RECIST 1.1 and attend visits on 12 weekly basis should continue to complete the questionnaires on 8 weekly basis until week 48. Assessments can be done in person or over the phone.

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

[k] 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, post discontinuation of study treatment need to be recorded.

[l] Optional tumour biopsy to be taken at objective radiological disease progression (so not at every treatment visit).

[m] Blood sample for biomarker analysis to be taken at randomisation and at objective radiological disease progression (so not at every treatment visit).

[n] Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 7 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment, at the time points shown in Table 2 during study treatment and at the 30 day follow up visit If results are positive the patient is ineligible/must be discontinued from study treatment immediately. The pregnancy test results need to be recorded in the patients' notes.

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

Visit Number	**Off treatment follow-up** Study treatment discontinued due to reasons other than disease progression	**2nd progression (PFS2) and Survival follow-up for patients who have discontinued study treatment due to disease progression:** • Objective Radiological progression • Clinical progression • CA-125 progression
	Follow up for 1st progression Tumour assessment visits every 8 weeks or 12 weeks[a]	Visits to occur every 12 weeks from the date of first progression
Visit Window	±7d	±7d
Blood sample for disease specific marker (CA-125)	X	
Tumour Assessment (CT or MRI according to RECIST v1.1) [a]	Every 8 weeks for 48 weeks and every 12 weeks thereafter until PD, one additional RECIST assessment required after PD declared by the investigator	
Adverse Events	X[i]	X[i]
ECOG performance status	X	X
EQ-5D-5L[b]	X	X[b]
FACT-O[b]	X	X[b]
Resource use[f]	X	
Subsequent cancer therapy following discontinuation of study treatment[c]	X	X
Tumour biopsy on progression (optional)[g]	X	

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

Visit Number	**Off treatment follow-up** Study treatment discontinued due to reasons other than disease progression	**2nd progression (PFS2) and Survival follow-up for patients who have discontinued study treatment due to disease progression:** • Objective Radiological progression • Clinical progression • CA-125 progression
	Follow up for 1st progression Tumour assessment visits every 8 weeks or 12 weeks[a]	Visits to occur every 12 weeks from the date of first progression
Blood samples for biomarker analysis on progression[h]	X	
Time to second progression		X
Survival[d,e]	X	X

[a] RECIST follow-up assessments will be performed as per the original schedule every 8 weeks (±1 week) during the first 48 weeks and every 12 weeks (±1 week) thereafter relative to date of randomisation. Patients who are determined to have progressed according to RECIST 1.1 criteria by the investigator will have one final RECIST assessment at the next scheduled RECIST visit in order to minimise bias in the BICR assessment in the event the investigator declares objective progression earlier than the BICR. 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 must be followed until RECIST disease progression. 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. Patients who are determined to have progressed according to RECIST 1.1 criteria by the investigator will have one final RECIST assessment at the next scheduled RECIST visit.

[b] FACT-O and EQ-5D will be collected at baseline, day 29, week 8, 16, 24, 32, 40 and 48 (+/- 1 week) from start of study treatment regardless of treatment discontinuation or disease progression. Patients, who have progressed as per RECIST1.1 and attend visits on 12 weekly basis, should continue to complete the questionnaires on 8 weekly basis until week 48. Assessments can be done in person or over the phone.

[c] 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 study treatment need to be recorded

[d] 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.

[e] 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

[f] In line with the RECIST assessments (every 8 or 12 weeks) until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose

[g] Optional tumour biopsy to be taken at objective radiological disease progression (so not at every off-treatment follow up visit)

[h] Blood sample for biomarker analysis to be taken at objective radiological disease progression (not at every off-treatment follow-up visit).

i Please refer to section 6.3.3

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 *gBRCA s*tatus will be screened for BRCA mutation and will start the study from screening Part1 and continue with Part 2 and Part 3, if applicable.

Patients with known *gBRCA* mutation (by central or local BRCA test) will start study from screening Part 2 and continue to Part 3.

All patients will be required to provide consent to supply a sample of their biological sample for entry into this study. This consent is included in the main patient informed consent form.

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 study treatment 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 Patients who have objective radiological disease progression but continue on study treatment

Patients should be discontinued from study treatment if they have objective radiological disease progression according to RECIST (see Appendix E), unless 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). These patients will continue on treatment following procedures as per the second column of Table 3 and will be followed for PFS2 and OS. Safety assessments can occur with the same frequency as the visits unless more frequent testing is clinically indicated.

4.3.2 Follow-up 30 day after last dose of investigational product (IP) (follow-up visit)

A follow-up visit should be conducted 30 days after the last dose of study treatment. 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 3 and Table 2).

4.3.3 Survival

Assessments for survival should be made every 12 weeks following objective radiological disease progression according to RECIST 1.1. 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 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 6.3.3.

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.

4.3.4 Second progression

Following objective progression, copies of the patient's radiological scans are no longer required to be sent for blinded independent central review. Patients will 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. RECIST measurements will not be collected for assessment of PFS2. The date of PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

4.3.5 Patient management post primary analysis

The data cut-off for the primary analysis will occur in January 2019 or at a minimum of 6 months after LSI, whichever is sooner.

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

Patients on study treatment will be followed for core safety assessments and disease progression (haematology, clinical chemistry, AEs/SAEs and concomitant medications (including any subsequent cancer therapy), study treatment dosing details, objective radiological disease progression according to RECIST1.1, and as per Table 2). These patients

should be followed according to routine clinical practice but visits should take place at least every 12 weeks.

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

After the primary analysis, central review of scans will no longer be required and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review.

HRQoL data will not be collected post primary analysis.

4.3.6 Patient management post final analysis

An additional PFS2 and OS analysis will only be conducted with further follow up if both ORR and PFS are statistically significant based on the primary analysis and the null hypotheses for PFS2 and/or OS are not rejected at the time of the primary analysis. The data-cut off for this additional analysis will be established when the OS data approximately 60% mature.

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

AstraZeneca will continue to supply olaparib after completion of this study until either olaparib is licenced in that country, or it is determined that the benefit to risk profile does not support continued development of olaparib, or the national health authority has deemed the drug not approvable. In all these scenarios, AstraZeneca will work with investigators on the proper transition of patients to alternative therapies if possible.

SAEs will continue to be reported to AstraZeneca Patient Safety Department, for any patients who continue on olaparib until 30 days after study treatment is discontinued, in accordance with Section 6.3.3. 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.

Drug accountability should continue to be performed until the patient stops study treatment 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 electronic Case Report Forms (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 (RECIST 1.1)

Baseline assessment will be performed no more than 28 days prior to study treatment start and as close as possible to study treatment start. Following the baseline assessment, subsequent tumour assessments according to RECIST 1.1 should be performed at the end of every 8 weeks (+/- 1 week) from randomisation for 48 weeks and every 12 weeks (+/- 1 week) thereafter. All CT/MRI scans will be sent to an AstraZeneca appointed Clinical Research Organisation (CRO) for blinded independent central review. All treatment decision will be based on investigator's assessment of the scans.

All patients should have RECIST assessments until documented evidence of objective radiological progression in accordance with RECIST 1.1, irrespective of treatment decisions (i.e., RECIST follow up until progression even if a patient discontinues study treatment prior to progression and/or receives a subsequent therapy prior to progression). Patients who are determined to have progressed according to RECIST 1.1 criteria by the investigator will have one final study RECIST assessment at the next scheduled RECIST visit in order to minimise bias in the BICR assessment in the event the investigator declares objective progression earlier than the BICR.

At baseline, the imaging modalities used for RECIST assessment will be 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. The methods of assessment of tumour burden used at baseline must be used at each subsequent follow-up assessment.

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

Anonymised copies of the scans are to be sent to an AstraZeneca appointed CRO for blinded independent central review.

All treatment decisions will be based on site assessment of scans.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of scheduled visit ± 1 week window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Patients will be evaluated until objective radiological disease progression by RECIST 1.1 as per the study schedule and then followed for second progression and survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

5.1.2 Tumour Evaluation

RECIST 1.1 criteria will 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 E.

Although CA-125 is measured in this study it will not be directly used for assessing objective response or progression and patients should be continued on treatment until objective radiological disease progression as defined by RECIST 1.1.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: 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 randomisation.

For patients with non-measurable disease only at baseline, categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR (complete response), PD (progression of disease), Non CR/Non PD or NE (not evaluable). A response of CR or PR will not require confirmation due to the randomized controlled study design as per the RECIST guidelines. However, a sensitivity analysis of confirmed CR or PR will be conducted.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTL (non-target lesion) 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.

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.

5.1.3 Central reading of scans

An independent review of all scans used in the assessment of tumours using RECIST 1.1 will be conducted. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed CRO for central analysis. Results of this independent review will not be communicated to investigators, and the management of patients will be based solely upon the results of the RECIST assessment conducted by the investigator. Please note that patients who are determined to have progressed according to RECIST 1.1 criteria by the investigator will have one final RECIST assessment at the next scheduled RECIST visit (8 or 12 weeks) in order to minimise bias in the BICR assessment in the event the investigator declares objective progression earlier than the BICR.

After the primary PFS analysis, central review of scans will no longer be required and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review.

The primary analysis for this study will be based on the blinded independent central review (BICR) of the radiological scans.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

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

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology and urinalysis will 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 C '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
B- Red Blood Cells count (RBC)	S/P-Alkaline Phosphatase (ALP)
Mean Cell Haemoglobin Concentration (MCHC)	S/P-Aspartate Transaminase (AST)
Mean Cell Volume (MCV)	S/P-Alanine Transaminase (ALT)
Mean Cell Haemoglobin (MCH)	S/P-Albumin
B-Leukocyte differential count (absolute count)	S/P-Potassium
B-Platelet count	S/P-Calcium, total
White Blood Cells (WBC) with absolute differential white cell count[1]	S/P-Sodium
	S/P GGT
Urinalysis (dipstick)	S/P urea or Blood Urea Nitrogen (BUN)
U-Hb/Erythrocytes/Blood	S/P – Protein, total
U-Protein/Albumin	Activated Partial Thromboblastin Time (APTT)[2]
U-Glucose	International Normalised Ratio (INR)[3]

[1] Neutrophils, lymphocytes, monocytes, eosinophils and basophils and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials are not available please provide % differentials.

[2] Coagulation will be performed if clinically indicated

[3] INR will be performed if clinically indicated unless the patient is receiving warfarin or acenocoumarol. Patients taking warfarin or acenocoumarol may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at baseline and at least once per week for the first month, then monthly if the INR is stable. This information must be recorded on the lab form of the eCRF.

5.2.1.1 Disease specific tumour marker samples (CA-125)

As part of the routine safety blood samples, all patients will supply blood sample for CA-125 (2 mL) for assessment at each time point indicated in Table 1, Table 2 and Table 3.

It is important to follow the assessment schedule as closely as possible. If CA-125 assessment is performed outside of scheduled visit ± 1 week window interval, every attempt should be made to assess the CA-125 at the scheduled time points. Patients will be evaluated until objective disease progression, based on progressive serial elevation of serum CA-125 according to the Gynecologic Cancer InterGroup criteria GCIG criteria (Further assessment of CA 125 post serological progression will be at the discretion of the investigator according to local clinical practice.

5.2.1.2 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be considered for patients with prolonged haematological toxicities as defined in Section 6.8.

At the discretion of a haematology consultant, bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the investigator for documentation on the Patient Safety database.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 5.2.1.

5.2.2 Physical examination

For timing of individual measurement refer to study schedule (see Table 1, Table 2, and Table 3).

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

5.2.3 ECG

ECGs are required within 7 days prior to starting study treatment and as clinically indicated afterwards. No repeat ECG is required at screening or baseline if the first ECG shows no clinically significant abnormalities.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If

there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

5.2.4 Vital signs

Vital signs will be performed during study treatment if clinically indicated.

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.

5.2.4.1 Pulse and blood pressure

Blood pressure and pulse rate will be measured preferably using a semiautomatic BP recording device with an appropriate cuff size after 10 minutes rest on a bed or seated on a chair. 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.

5.2.4.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in the Study Schedule (see Table 1, Table 2, and Table 3).

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

5.2.5 Other safety assessments

5.2.5.1 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 7 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment, at the time points shown in Table 2 during study treatment and at the 30 day follow up visit. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from study treatment immediately.

5.3 Other assessments

5.3.1 Patient reported outcomes

Patient Reported Outcomes (PRO), an umbrella term referring to all outcomes and symptoms, are directly reported by the patient. Patient Reported Outcomes have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered in this study: FACT-O, CTSQ-16, EQ-5D-5L and PGIC. Each is described below.

5.3.1.1 FACT-O

Patient-reported health-related quality of life (HRQoL) will be assessed using the FACT-O questionnaire, see Appendix G. 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 endpoint 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.

5.3.1.2 CTSQ-16

The CTSQ-16 is a validated 16-item questionnaire measuring 3 domains related to patients' satisfaction with cancer therapy: Expectations of Therapy (ET), Feelings about Side Effects (FSE), and Satisfaction with Therapy (SWT) (see Appendix G). The CTSQ-16 was developed for use in a wide range of cancer types and stages, and is specific to adult patients receiving cancer therapy. In particular, this instrument can be used for both intravenous (IV) and oral cancer therapy assessments.

5.3.1.3 EQ-5D-5L

The EQ-5D is a standardised measure of health status developed by the European Quality of Life (EuroQoL) Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQoL Group 1990), see Appendix G. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty (EuroQoL Group 2013). Since 2009, the EuroQoL group has been developing a more sensitive version of the EQ-5D (the EQ-5D-5L), which expands the range of responses to each dimension from 3 to 5 levels of increasing severity (Herdman et al 2011). Preliminary studies indicate that the 5 level (5L) version improves upon the properties of the 3 level (3L) measure in terms of reduced ceiling effect, increased reliability, and an improved ability to differentiate between different levels of health (Pickard et al 2007, Janssen et al 2008, Janssen et al 2008b). The patient will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale (VAS), where the patient will be asked to rate current health status on a scale of 0 to 100, with zero being the worst imaginable health state.

5.3.1.4 PGIC

Patient Global Impression of Change is a one-item instrument asking patients at the end of treatment to assess on a 7-point scale to what extent they perceive that their main symptoms

under treatment have changed since the beginning of treatment, where -3 implies that symptoms are very much worse, 0 implies no change, and +3 that symptoms are very much improved.

5.3.1.5 Administration of PRO questionnaires

The PROs will be completed at given time points as described in the study schedule (Table 2, and Table 3). Paper questionnaires will be given to the patient at baseline, at Day 29, week 8, 16, 24, 32, 40 and 48 relative to the day of randomisation. For all PROs, patients are to complete the questionnaire during their clinic visit. The site staff will enter the information directly into the eCRF.

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 study monitor 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:

- It 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
- It must be completed in private by the patient
- 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 questionnaire (e.g., is blind or illiterate) the questionnaire may be read out by trained clinic staff and responses recorded
- On completion of the questionnaire it should be handed back to the person responsible for questionnaires who should check for completeness
- Only 1 answer should be recorded for each question

5.3.2 Health economics

Resource use will be captured including inpatient admissions, Intensive Care Unit and length of stay in hospital.

5.4 Pharmacokinetics

PK sampling is to be performed in a subset of patients from the olaparib treatment arm.

5.4.1 Pharmacokinetic samples (subset of patients)

Approximately 65 evaluable patients (i.e., those that have been randomised to olaparib) randomised at pre-agreed sites will have PK assessment samples taken.

In order to assess the potential influence of ethnicity/race on olaparib, centres are requested to consider favouring Black American, Asian and Hispanic patients for this PK subset population.

Table 5 Pharmacokinetic samples

Visit Number	**2**	**3**	**4**	**5**	**6**
Day	1	8	15	22	29
Sampling time	Pre dose and 1 hr ± 5 min post dose				Pre-dose; 0.5-1 hour, 1-3 hours 3-6 hours, and 6-12 hours post dose
Blood sample for PK analysis (*Subset of patients*)	X				X

5.4.2 Collection of samples

Blood samples for determination of olaparib concentrations in plasma will be taken at the times presented in Table 5.

To ensure that the assessments are carried out such that the PK sampling is performed within the required sampling windows, it will be necessary to arrange the assessment procedures so that the PK assessments fall at/around the correct timing. The actual time of dosing and collection of all PK samples must be recorded as described below:

On Day 1 the times of the pre-dose and 1 hour ± 5 min post dose PK samples must be recorded along with the times of both the morning and evening study treatment doses.

On Day 29, the morning dose of study treatment should not be taken at home, but must be taken after the pre-dose PK sample has been taken. The times of the pre-dose and all of the post dose PK samples and the times of both the morning and evening doses of study treatment

must be recorded. In addition to the dosing times on the PK day, it is important to record the previous day's morning and evening doses of study treatment (i.e. Day 28).

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

NOTE: all post-dose samples are timed from the first dose of olaparib of the day.

5.4.3 Determination of drug concentration

Samples for determination of olaparib concentration in plasma will be analysed by Covance on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

5.4.4 Storage and destruction of pharmacokinetic samples

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

PK samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

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

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 Biomarker analysis

5.6.1 Collection of blood sample for Myriad germline *BRCA1* and *BRCA2* testing

All patients must have a known deleterious or suspected deleterious BRCA mutation to be randomised; this may have been determined prior to study entry or may be assessed as part of the enrolment procedure for the study (via Myriad).

For patients that can be randomised to the study on the basis of a pre-existing known BRCA mutation test result, a blood sample for a confirmatory BRCA mutation test by Myriad must be taken once the patient has consented to the study. Should the result from the Myriad test

indicate the patient does not have a deleterious or suspected deleterious BRCA mutation, the patient can continue in the study and can continue to receive their allocated study treatment. Residual blood (or its derivatives) may be used to develop and validate future BRCA companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of disease recurrence (including BRCA mutation status and its role in response).

For patients who meet the trial eligibility criteria, but do not know their BRCA mutation status, a blood sample for the Myriad BRCA test can be taken once all local ethical procedures for such testing have been completed. When the result from the Myriad test indicates the patient does have a deleterious or suspected deleterious BRCA mutation, the patient can be randomised into the study. Residual blood (or its derivatives) may be used to develop and validate future BRCA companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of disease recurrence (including BRCA mutation status, its role in response and mutation status of other genes known/predicted to have a role in ovarian cancer).

For blood volume see Section 5.9.

5.6.1.1 Guidance for *BRCA* testing of patients with unknown *BRCA* status

Patients that do not know their *BRCA* status, but meet all other eligibility criteria must have a Myriad test prior to randomisation in to the study. If the result shows that the patient has a deleterious/suspected deleterious *gBRCA* mutation, the patient can then be randomised to the study. Patients will need to have met the local ethical requirements for such genetic tests (e.g., genetic counseling) prior to the test procedure.

The following clinicopathological features are known to be associated with an increased probability of *BRCA* mutations:

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

2. High grade serous ovarian cancer

The patient must meet all the eligibility criteria in Sections 3.1 and 3.2 with an asterisk prior to having the blood sample taken for the Myriad *gBRCA* status test. The patient's consent to the use of donated biological samples is mandatory. The aforementioned clinicopathological features (family history of cancer, ethnicity, age and grade of cancer) are collected in CRF.

5.6.2 Collection of sample for assessment of current and future *BRCA* assay(s)

As part of the requirements for the development of a companion diagnostic for olaparib it will be necessary to collect a second blood specimen from all patients who submit samples for Myriad testing if allowed by local regulations. These samples will be stored for subsequent analysis to enable development and validation of a companion diagnostic for olaparib. Where allowed this includes samples from those patients who were shown not to have a deleterious

or suspected deleterious *BRCA1* or *BRCA2* mutation. Residual blood (or its derivatives) may be used to develop and validate future BRCA companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of disease recurrence (including BRCA mutation status, its role in response and mutation status of other genes known/predicted to have a role in ovarian cancer).

For blood volume see Section 5.9.

5.6.3 Collection of biomarkers biological samples

Biological samples (archived tumour samples and blood 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:

- Mandatory: Archived tumour sample

  Formalin fixed, paraffin embedded (FFPE) tumour sample from the primary or recurrent cancer must be available for central testing. If there is not written confirmation of the availability of an archived tumour sample prior to enrolment the patient is not eligible for the study.

- Optional: Tumour biopsy at baseline and/or disease progression

  The baseline biopsied tumour should not be assessed as a target lesion as part of the RECIST assessments if there are other lesions available. The biopsy should be taken after the baseline scan has been performed.

- Mandatory: Blood sample for biomarker analysis

  Two 6 mL blood samples (one plasma and one serum) will be collected from all patients at randomisation and at progression for exploratory biomarker work.

5.6.4 Storage, re-use and destruction of biomarkers 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 Pharmacogenetics

5.7.1 Collection of pharmacogenetics

The patient's consent to participate in the pharmacogenetic research components of the study is mandatory.

The blood sample for genetic research will be obtained from the patients at Visit 2. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study.

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

5.7.2 Storage, re-use and destruction of pharmacogenetics

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. If allowed by local regulations 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. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

5.8 Labelling and shipment of biological samples

The Principal Investigator at each centre 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 B International Air Transport Association (IATA) 6.2 Guidance Document.

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

5.8.1 Chain of custody of biological samples

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

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

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

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

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

5.8.2 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.

Prospective Myriad *BRCA* sample for patients with unknown *BRCA* status: As collection of the biological sample is an integral part of the study, then the patient is withdrawn from further study participation.

Archival tumour sample: Although mandatory, the patient may continue in the study if the patient is already randomised.

Tumour biopsy samples: As collection of the biological samples is an optional part of the study, then the patient may continue in the study.

Blood samples for biomarker analysis: Although mandatory, the patient may continue in the study if the patient is already randomised.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca or designated 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.

5.9 **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 and if the patient is in the subset having PK samples taken. However the volume of blood to be drawn from each patient (including for PK samples) during screening and up to Day 29 should not exceed 150 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 210 mL.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore patient to site-specific change.

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 6.

Table 6 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	**Mths 2-6** No. of samples	**Treatment Discontinuation visit and 30 day follow-up visit** No. of samples	**Objective radiological disease progression** No. of samples	**Total vol. (mL)**
Safety	Clinical chemistry (locally assessed)	5	1	5	1(x4)	1(x2)		**60**
	Haematology (locally assessed)	5	1	5	1(x4)	1(x2)		**60**
Whole Blood sample: Prospective Myriad *BRCA* test for patients with unknown *BRCA* status or for confirmation of *BRCA* status for those with previous results		10	1					**10**
Whole blood sample For assessment of current and future *BRCA* mutation assay(s)		10	1					**10**
Blood samples (plasma and serum) for biomarker analysis		12		1			1	**24**
Serum pregnancy test		Site dependent	Site may use urine instead	Site may use urine instead				
Blood sample for CA-125 (locally assessed)		2	1	1(x2)	1(x4)	1(x1) (only treatment discontinuation visit)		**16**
Pharmacokinetic (Blood samples processed to plasma & frozen)		2		7				**14**
Optional exploratory Pharmacogenetics		9		1				**9**
Total volume (ml)			**32**	**89**	**48**	**22**	**12**	**203**

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 A to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 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.

6.3.2 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.

6.3.3 Adverse events after the 30 day follow-up period

For Pharmacovigilance purposes and characterisation, any case of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported to AstraZeneca Patient Safety whether it is considered a non-serious AE [eg non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for overall survival if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases. A Questionnaire will be sent to any investigator reporting MDS/AML or new primary malignancy 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 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).

6.3.4 Variables

The following variables will be collected 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 AE

For each episode on an adverse event, all changes to the CTCAE grade attained as well as the highest attained CTC 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).

6.3.5 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 A to the Clinical Study Protocol.

6.3.6 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.

6.3.7 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECG abnormalities should therefore only be reported as AEs if one of the following is met:

- Any criterion for an SAE is fulfilled
- Causes study treatment discontinuation
- Causes study treatment interruption
- Causes study treatment dose reduction
- The investigator believes that the abnormality should be reported as an AE

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

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

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

6.3.8 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 C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.9 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.

6.3.10 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.

6.3.11 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.

6.3.12 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.

6.4 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 in a SAE Report Form.

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 for the AstraZeneca drug.

6.5 **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. The recommended Phase III clinical trials dose for olaparib tablet is 300 mg twice daily.

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 6.4. For other overdoses, reporting must occur within 30 days.

6.6 **Pregnancy**

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

6.6.1 Maternal exposure

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

The outcomes of any conception occurring from the date of the first dose of study medication until 3 months after the last dose of study medication must be followed up and documented.

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 1day 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 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

6.6.2 Paternal exposure

Not applicable.

6.7 Management of IP related toxicities

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step.. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment should be discontinued.

Once dose is reduced, escalation is not permitted.

6.8 **Management of haematological toxicity**

6.8.1 Management of anaemia

Haemoglobin	*Action to be taken*
Hb < 10 *but* **≥ 8 g/dl (CTCAE Grade 2)**	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 4 weeks. If repeat Hb**< 10** *but* **≥ 8 g/dl**, dose interrupt until Hb ≥ 10 g/dl for max of 4 weeks and upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step may be considered
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib until improved to Hb ≥ 10 g/dl. Upon recovery dose reduce olaparib to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

Common treatable causes of anaemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence) , refer to Section 6.8.3 for the management of this.

6.8.2 Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	*Study treatment dose adjustment*
CTCAE gr 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE gr 3-4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE gr 3-4 occurrence, dose reduce olaparib to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local

hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse), refer to Section 6.8.3.

6.8.3 Management of prolonged haematological toxicities while on study treatment

If a patient develops prolonged haematological toxicity such as:

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

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Study treatment should be discontinued if blood counts do not recover to CTC gr 1 or better within 4 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

6.9 Management of non-haematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the study monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg bd as a first step and to 200 mg bd as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

6.9.1 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

6.9.2 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered eg dopamine receptor antagonist, antihistamines or dexamethasone.

6.9.3 Interruptions for intercurrent non-toxicity related events

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

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

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

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered. Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

Table 7 Dose reductions for study treatment

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300mg twice daily	250mg twice daily	200mg twice daily

7 MANAGEMENT OF TOXICITY OF CHEMOTHERAPY

Dosing and treatment regimen information for weekly paclitaxel, topotecan, PLD and gemcitabine can be found in the local package inserts supplied with the drug. During patients' participation in the study actions for chemotherapy related toxicity should comply with the prescribing information for toxicity management and dose reduction.

8 STUDY GOVERNANCE AND OVERSIGHT

8.1 Data Monitoring Committee

This study will use an external Independent Data Monitoring Committee (IDMC) to perform interim reviews of accumulating study safety data. This committee will be composed of therapeutic area experts and a statistician, who are not employed by AstraZeneca, and do not have any major conflict of interest. Following the review the IDMC will recommend whether the study should continue unchanged, be terminated, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca. The report will only include the recommendation and any potential protocol amendments. It will not contain any unblinded information. A separate IDMC charter will be developed which will contain details of the IDMC members and clearly define the responsibilities of the IDMC.

9 INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

9.1 Identity of investigational product(s)

Table 8 Identity of investigational product

Investigational product[a]	Dosage form and strength	Manufacturer
Olaparib	Tablet – 150mg and 100mg	Soliqs or AbbVie on behalf of AstraZeneca

[a] Descriptive information for olaparib can be found in the olaparib Investigator's Brochure

Paclitaxel, topotecan, pegylated liposomal doxorubicin and gemcitabine will be sourced locally. Only under exceptional circumstances when this isn't feasible these chemotherapies will be supplied through AstraZeneca. All comparator drugs do not need to be available for a site to enrol a patient as long as the comparator of choice is available. Descriptive information for the chemotherapy can be found in the local package inserts supplied with the drug. If AstraZeneca is centrally supplying these drugs the package insert may not be in the language of the receiving market. In this case, the investigator should use the local package insert information and local standard practices for use of these drugs.

9.2 Dose and treatment regimens

For all centres, olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain sufficient medication for at least 28 days plus overage. Olaparib will be dispensed to patients on Day 1 and every 28 days until week 48 and then every 12 weeks thereafter until the patient completes the study, withdraws from the study or closure of the study.

Patients randomised to olaparib will administered their randomised tablets orally at a dose of 300 mg twice daily.

Olaparib is available as a film-coated tablet containing 150mg or 100mg of olaparib. Tablets are to be taken orally, twice daily (bd). Doses of olaparib should be taken at the same times each day approximately 12 hours apart. All doses should be taken with approximately 240 mL of water. The IP tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

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

There is no maximum duration for taking IP treatment. Patients will continue with olaparib until objective disease progression (determined by RECIST 1.1), however patients may continue with olaparib as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

For details about dose interruption and reduction please refer to Sections 6.7, 6.8, and 7.

9.3 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 "Study Participation Card". For emergency purposes the patient must be in possession of the emergency contact details at all times.

9.4 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.

9.5 Compliance

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

Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer olaparib. Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF.

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

9.6 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.

9.7 Concomitant and other treatments

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, 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 as per Table 1, Table 2, and Table 3.

9.7.1 Medications that may NOT be administered

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.

9.7.1.1 Olaparib and drug-drug interaction

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

Effect of Other Drugs on Olaparib

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

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

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

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

In addition, in vivo data have shown that co-administration with rifampicin (a known CYP inducer) reduces olaparib AUC by an average of 87%. Therefore, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4/5 inducers should be avoided:

- phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbital, nevirapine, modafinil and St John's Wort (*Hypericum perforatum*)

For patients taking any of the above, the required wash-out periods prior to starting study treatment for phenobarbital is 5 weeks, and for any of the others, 3 weeks.

After randomisation if the use of any potent inducers or inhibitors of CYP3A4/5 are considered necessary for the patient's safety and welfare, the investigator must contact the Study Physician. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

In vitro olaparib is a substrate for the efflux transporter Pgp. Clinical studies to evaluate the impact of specific Pgp inhibitors and inducers have not been conducted; however based on the physical and absorption, distribution, metabolism and excretion properties of olaparib, there is a low risk that a Pgp modulator could significantly alter systemic exposure to olaparib

Effect of Olaparib on Other Drugs

Olaparib can inhibit CYP3A4 and UGT1A1 *in vitro*.. Using basic models 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 (GI) tract. However, PBPK modelling predicted olaparib to be a weak CYP3A inhibitor in vivo and did not predict olaparib to be a UGT1A1 inhibitor in vivo. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (eg, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (eg irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine).

Induction of CYP1A2, 2B6 and 3A4 has been shown *in vitro* with CYP3A4 being most likely to be induced to a clinically relevant extent. Based on an evaluation using enzyme activity, olaparib was not considered an inducer of CYP2C9 and 2C19. It cannot be excluded that olaparib upon co administration may reduce the exposure to substrates of these metabolic

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

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

9.7.1.2 Anticoagulant Therapy

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 carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

9.7.1.3 Anti-emetics/Anti-diarrhoeals

From screening part 2 onwards, should a patient develop nausea, vomiting and / or diarrhoea, then these symptoms should be reported as AEs (see section 6.3.6) and appropriate treatment of the event given.

9.7.1.4 Palliative radiotherapy

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

9.7.1.5 Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. 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 4 weeks prior to beginning study treatment.

9.7.1.6 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.

9.8 Post Study Access to Study Treatment

No plans to provide olaparib after completion of the study treatment.

10 STATISTICAL ANALYSES

10.1 Statistical considerations

Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first patient randomised and any subsequent amendments will be documented, with final amendments completed prior to database lock.

10.2 Sample size estimate

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

The primary endpoint of the study is ORR. With at least 223 subjects, recruited 2:1 olaparib: chemotherapy, the study will have >80% power to show a statistically significant difference in ORR at the two-sided 5% level, assuming a response rate of 25% on the chemotherapy arm and at least 45% on the olaparib arm for subjects with measurable disease at baseline accoridng to BICR. It is anticipated that approximately 90% of subjects will have measurable disease at baseline according to BICR and therefore to ensure adequate power, the sample size will have at least 250 subjects.

It is anticipated that the study recruitment period will be approximately 40 months and that the data-cut off for the primary analysis will occur in January 2019 or at a minimum of 6 months after LSI, whichever is sooner. This is to ensure sufficient patient follow-up to characterize duration of response (DoR) and satisfy a regulatory committment. No further analyses of ORR or PFS are planned beyond this point unless requested by Health Authorities.

10.3 Definitions of analysis sets

Table 9 gives a summary of outcome variables and analysis populations.

10.3.1 Full analysis set

The full analysis set (FAS) will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS).

10.3.2 Measurable disease analysis set (MDAS)

The measurable disease analysis set (MDAS) includes all patients in the FAS with measurable disease at baseline (as per RECIST 1.1):

- Measurable disease at baseline for the primary analysis is determined using BICR,

- For reporting the investigator response, the measurable disease analysis set will be determined using the investigator reported measurable disease at baseline

10.3.3 Safety analysis set

All patients who received at least one dose of randomised study treatment, olaparib or chemotherapy, will be included in the safety analysis set. If a patient receives at least one dose of olaparib study treatment they will be summarised in the olaparib arm for safety summaries (e.g. olaparib arm will include patients randomised to olaparib who receive at least one dose of olaparib or chemotherapy patients who receive at least one dose of olaparib study treatment in error at any time). If a patient randomised to olaparib receives only chemotherapy treatment then they will be summarised as part of the chemotherapy arm.

Table 9 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data	
- Primary : ORR by BICR	Measurable disease (MDAS)
- Secondary : PFS (by BICR), PFS2, OS, time to earliest progression by RECIST 1.1, CA-125 or death, CA-125 response, TFST, TSST, TDT, symptom/QoL endpoints	FAS
Duration of Response (DoR) by BICR	Measurable disease (MDAS)
Demography	FAS
Safety Data	
- Exposure	Safety
- Adverse Events	Safety
- Lab measurements	Safety
- Vital Signs	Safety

10.4 Outcome measures for analyses

10.4.1 Calculation or derivation of efficacy variable(s)

At each visit patients will be programmatically assigned a RECIST visit response of CR, PR, SD, PD, NE depending on the status of their disease compared to baseline and previous assessments, based on the BICR review. This will be repeated using the investigator assessed RECIST data.

10.4.1.1 Primary endpoint

Objective Response Rate (ORR)

Best overall RECIST response (BoR) is calculated based on the overall visit responses from each RECIST assessment, described in Appendix E. It is the best response a patient has had during their time in the study up until RECIST progression or the last evaluable assessment in the absence of RECIST progression.

Categorisation of best overall response will be determined programmatically based on the RECIST 1.1 criteria (Appendix E) for the BICR data, using the following response categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) and not evaluable (NE).

Best overall response will be determined programmatically from the time point response using BICR data. In addition, this will also be reported using investigator-recorded assessment.

For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 8 weeks +/- 1 week, i.e. at least 49 days (to allow for the assessment window), after randomisation. For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

For patients whose disease progression event is death, BoR will be calculated based on data up until the last evaluable RECIST assessment prior to death.

For patients who die with no evaluable RECIST assessments, if the death occurred ≤17 weeks (i.e. 16 weeks ±1 week) after randomisation then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurred > 17 weeks (i.e. 16 weeks ±1 week) after randomisation then BoR will be assigned to the non-evaluable (NE) category.

Progression events that have been censored due to them being >126 days (i.e. 16 weeks ± 7 days) after the last evaluable assessment will not contribute to the BoR derivation.

A patient will be classified as a responder if the RECIST 1.1 criteria for a CR or PR are satisfied at any time up to and including the defined analysis cut-off point. For each treatment group, the objective response rate (ORR) is the number of patients with a CR and PR divided by the number of patients in the measurable disease analysis set (MDAS). Only patients with measurable disease at enrolment can achieve an objective response of CR or PR which will not require confirmation due to the randomized controlled study design as per the RECIST guidelines. However, a sensitivity analysis of confirmed CR or PR will be conducted.

10.4.1.2 Secondary endpoints

10.4.1.2.1 Time from randomisation to first progression (PFS)

The PFS endpoint is defined as the time from randomisation until the date of objective radiological disease progression according to RECIST 1.1 or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from randomised 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 RECIST 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 RECIST assessment. Given the scheduled visit assessment scheme, for the first 48 weeks from randomisation two missing visits will equate to more than 18 weeks since the previous RECIST assessment, allowing for early and late visits. After 48 weeks, two missing visits will equate to more than 26 weeks. 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 (17 weeks allowing for visit window).

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

(a) The date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or for either reviewer where both select PD as time point response and there is no adjudication for BICR data.

(b) For investigational site assessments, date of progression will be determined based on the earliest of the RECIST assessment/scan dates of the component that triggered the progression.

(c) When censoring a patient for PFS the patient will be censored at the **latest** of the RECIST 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 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.

The PFS analysis will be based on the blinded independent central review (BICR) of the radiological scans. The BICR will be based on all RECIST assessment scan data provided by investigators, including the final RECIST assessment obtained from patients after progression has been determined according to RECIST 1.1 criteria by the investigator. A charter for the BICR will be developed in advance of the start of the study. A sensitivity analysis based on

the programmatically derived PFS based on investigator-recorded assessments will be carried out.

10.4.1.2.2 Time from randomisation to second progression (PFS2)

Time from randomisation to second progression is defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the PFS endpoint 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, clinical, CA-125 progression or death. Second progression status will be reviewed every 12 weeks following the progression event used for the PFS endpoint (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 progression assessment date if the patient has not had a second progression or death).

10.4.1.2.3 Overall Survival

Overall survival is defined as the time from the date of randomisation 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 date of data cut-off (DCO) date 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.

10.4.1.2.4 Time to earliest progression by RECIST 1.1 or CA-125 or death

Progression or recurrence based on serum CA-125 levels will be defined on the basis of a progressive serial elevation of serum CA-125, according to the following GCIG criteria:

- Patients with elevated CA-125 pre-treatment (i.e. greater than the upper limit of normal (ULN):

    (a) If CA-125 does not fall to within the normal range whilst on treatment then there must be evidence of CA-125 greater than, or equal to, 2 times the nadir value in the 28 day period before day 1 on 2 occasions at least 1 week apart.

    (b) Where CA-125 does fall to within the normal range whilst on study treatment (and the patient has not already progressed by way of (a) above) then there must be evidence of CA-125 greater than, or equal to, 2 times the ULN on 2 occasions at least 1 week apart.

- Patients with CA-125 in the normal range pre-treatment must show evidence of CA-125 greater than, or equal to, 2 times the ULN on 2 occasions at least 1 week apart.

- CA-125 progression will be assigned the date of the first measurement that meets the criteria as noted.

Time to progression by RECIST or CA-125 progression or death is defined as the time from randomisation to the earlier date of RECIST (based on BICR) or CA-125 progression or death by any cause.

Patients without a CA-125 progression or a RECIST progression who are still alive at the time of analysis will be censored at the time of their last evaluable RECIST assessment or their last available CA-125 measurement, whichever is the earliest at the time of the analysis. Since CA-125 is assessed more frequently than RECIST the two missed visit rule is based upon the RECIST schedule. Therefore if a patient dies, has RECIST progression or has CA-125 progression after two or more missed RECIST assessments, then the patient will be censored using the last evaluable RECIST assessment where CA-125 was also collected. This will be defined as a RECIST assessment where the date of CA-125 sample is +/- 11 days (note the earliest date of the RECIST/CA-125 assessment will be used.).

If only one assessment is missing during this period, no censoring is required. Patients that do not have any evaluable RECIST assessments or any CA-125 results post-randomisation will be censored at the date of randomisation.

10.4.1.2.5 Duration of response (DoR)

Duration of response (DoR) will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

If a patient does not progress following a response, then their duration of response will use the PFS censoring date as the date at which that patient is censored for DoR.

10.4.1.2.6 Time to Response (TTR)

The time to response is defined as the time from randomisation until the date of first documented response. The date of first documented response should coincide with that used for the DoR endopint.

Time to response will not be defined for those patients who do not have a documented response.

10.4.1.2.7 GCIG CA-125 response

GCIG CA-125 response will be based on the GCIG criteria (Rustin et al 2004). Patients will be evaluable for CA-125 response if:

- a pre-treatment CA-125 level (taken within 2 weeks prior to starting treatment) is at least twice the upper limit of normal, and
- there is no more than a 10% fall in CA-125 between the two pre-treatment samples

- the same assay method is used for each sample from the same patient

A response according to CA-125 will be considered to have occurred if there is at least a 50% reduction in CA-125 levels from the last pre-treatment sample. The response must be confirmed and maintained for at least 28 days. The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response. Note the GCIG criteria are not validated for this trial population.

10.4.1.2.8 Time to first subsequent chemotherapy or death (TFST)

As a supportive summary to PFS, time to start of first subsequent chemotherapy or death will be assessed. Time to first subsequent chemotherapy or death is defined as the time from the date of randomisation to the earlier of first subsequent chemotherapy 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 chemotherapy.

10.4.1.2.9 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 randomisation 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.

10.4.1.2.10 Time to second subsequent chemotherapy or death (TSST)

As a supportive summary to PFS2, time to start of second subsequent chemotherapy or death will be assessed. Time to second subsequent chemotherapy or death is defined as the time from the date of randomisation 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.

10.4.1.2.11 FACT-O

Patient-reported health-related quality of life (HRQoL) will be assessed using the FACT-O questionnaire (Basen-Enquist K et al 2001). 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 endpoint for health-related quality of life analysis will be the Trial Outcome Index (TOI), (Cella D et al 1993) 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 at baseline, at Day 29 then in line with the RECIST assessments every 8 weeks (+/- 1 week) up to Week 32 (8 months) regardless of treatment discontinuation or disease progression.

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), functional well being (FWB) and 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 summarized 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 (Osoba et al 2005).

The population for analyses of HRQoL (TOI) will include a subset of the FAS population who have baseline TOI score.

The definitions of the visit response for Health Related QoL are outlined below (Table 10).

Best Overall TOI improvement (improvement in the absence of subsequent cancer therapy) will be defined as a change from baseline in the TOI of +10 points or more (Osoba et al 2005) sustained for at least 28 days, the denominator consisting of a subset of the FAS 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 randomisation up to the earliest

of starting any subsequent cancer therapy or death. Therefore, the following criteria will be used to assign a best overall score response for each patient based on the individual visit responses (Table 11).

Table 10 Health Related QoL Visit Response

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

Table 11 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 % 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.

10.4.2 Calculation or derivation of safety variable(s)

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs and ECG. These will be collected for all patients. Appropriate summaries of these data will be presented.

10.4.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca or designated CRO medically qualified expert will review the list of AEs that were not reported as SAEs and 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.

10.4.3 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic (PK) analysis of the plasma concentration data for olaparib will be performed at AstraZeneca R&D or by a CRO identified by AstraZeneca R&D. The actual sampling times will be used in the PK calculations. Non-linear mixed effects modelling (NONMEM) will evaluate the pharmacokinetic characteristics of olaparib, quantify variability in the pharmacokinetics, identify demographic or pathophysiological covariates which may explain the observed variability, estimate steady state Cmax, AUC and Cmin and explore exposure-response relationships.

10.4.4 Calculation or derivation of pharmacodynamic variable(s)

Not applicable.

10.4.5 Calculation or derivation of pharmacogenetic variables

To be defined in an exploratory analysis plan.

10.4.6 Calculation or derivation of health economic variables

10.4.6.1 Resource Utilisation

Frequency of resource use including type, length of stay and procedures undertaken, and the primary symptom/reason for the hospitalisation or hospital attendance will be estimated.

10.4.6.2 EQ-5D-5L

The EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care.

The EQ-5D-5L index comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible five options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/ extreme problems). A unique EQ-5D health state is referred to by a five digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the five dimensions. This data will be converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (the base case will be the UK valuation set, with other country value sets applied in

scenario analyses). Where values sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied. In addition to the descriptive system, respondents also assess their health today on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

The evaluable population will comprise all patients who receive study treatment as safety analysis set and have a baseline EQ-5D-5L assessment.

10.5 **Methods for statistical analyses**

The treatment comparison is olaparib 300 mg bd versus physician's choice of chemotherapy.

Results of all statistical analysis will be presented using a 95% confidence interval and 2-sided p-value.

The following table details which endpoints are to be patient to formal statistical analysis, together with pre-planned sensitivity analyses making clear which analysis is regarded as primary for that endpoint.

Table 12 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses

Endpoints Analysed	Notes
ORR (Objective response rate)	Primary analysis: stratified logistic regression using BICR assessment in the MDAS Sensitivity / supportive analyses: 1) Ascertainment bias analysis: Stratified logistic regression using investigator assessments in the MDAS 2) Stratified logistic regression based on BICR for all patients with evaluable disease. Patients with evaluable disease include all of those in the MDAS and patients with non-target lesions at baseline and non-measurable disease at baseline. (Only required if the evaluable disease population differs from the MDAS.). 3) Stratified logistic regression based on BICR for all patients in the FAS. (Only required if the FAS population differs from the MDAS). 4) Stratified logistic regression based on responses confirmed by BICR in the MDAS. 5) Stratified logistic regression based on responses confirmed by investigator assessment in the MDAS. 6) Deviation bias (if meaningful to do): stratified logistic regression using BICR assessments. 7) Supportive: CA-125 response per treatment arm (descriptive only); CA-125 and/or RECIST response per treatment arm (descriptive only) based on BICR for RECIST

Table 12 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses

Endpoints Analysed	Notes
PFS (Time from randomisation to first progression or death)	Primary analysis: Stratified log-rank test using BICR assessments Sensitivity/supportive analyses[a]: 1) Evaluation time bias analysis; stratified log-rank test using BICR assessments 2) Attrition bias analysis (using alternative censoring rules); stratified log-rank test using BICR assessments 3) Ascertainment bias analysis; stratified log-rank test using investigator assessments 4) Deviation bias (if meaningful to do); stratified log-rank test using BICR assessments
PFS2 (Time from randomisation to second progression or death)	Primary analysis: stratified log rank test based on investigator assessment of second progression
Overall Survival (Time from randomisation to death due to any cause)	Primary analysis: stratified log-rank test Supportive analysis: KM plot of time to censoring for OS
Time to earliest progression by RECIST 1.1 or CA-125 or death	Primary analysis: stratified log-rank test using BICR assessment
TFST (Time to first subsequent therapy or death)	Stratified log rank test using eCRF data
TSST (Time to second subsequent therapy or death)	Stratified log rank test using eCRF data
TDT (Time to study treatment discontinuation or death)	Stratified log rank test using eCRF data
Change from baseline in TOI score	Primary: Mean change from baseline in TOI score analysed by MMRM Supportive: Proportion improved (in the absence of subsequent cancer therapy) in TOI score analysed using logistic regression

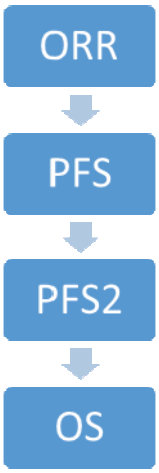
10.5.1 Multiplicity strategy for primary and key secondary endpoints

In order to describe the nature of the benefits of olaparib maintenance treatment, ORR, PFS, PFS2, and OS will be tested at a 2-sided significance level of 5%.

However, in order to strongly control the type I error at 2.5% 1-sided, a multiple testing procedure will also be employed across the primary endpoint and secondary endpoints intended for key label claims (i.e. ORR, PFS, PFS2 and OS). There is no requirement to adjust for multiplicity due to ORR or PFS interim analyses, since there are no planned interim ORR or PFS analyses with the opportunity to make an early claim of efficacy.

A hierarchical testing strategy will be employed where ORR is tested first using the full test mass (full test mass = alpha 5% 2 sided) and key secondary endpoints of PFS, PFS2 and OS will then be tested using a multiple testing procedure with a recycling strategy (i.e., the MTP will recycle the test mass to the endpoint not yet rejected in the hierarchy outlined in Figure 3).

Figure 3 Multiple Testing Procedure



PFS will only be tested if the null hypothesis (of no difference) for ORR is rejected. PFS2 will only be tested if the null hypothesis (of no difference) is rejected for both ORR and PFS. OS will only be tested if the null hypothesis (of no difference) is rejected for ORR, PFS and PFS2. An additional PFS2 and OS analysis will only be conducted with further follow up (~60% OS events) if both ORR and PFS are statistically significant based on the primary analysis and the null hypotheses for PFS2 and/or OS are not rejected at the time of the primary analysis. If an additional analysis is conducted for PFS2 and OS, to control for multiple testing due to an interim and final analysis a Lan DeMets spending function (Lan and DeMets 1983) that approximates an O'Brien Fleming approach will be used to account for multiplicity.

10.5.2 Analysis of the primary variable(s)

10.5.2.1 Objective Response Rate (ORR)

The data cut-off for the primary analysis will occur in January 2019 or at a minimum of 6 months after LSI, whichever is sooner. No further analyses of ORR are planned beyond this point unless requested by Health Authorities.

For each treatment arm, best overall RECIST response (BoR) will be summarised by n (%) for each category (CR, PR, SD, PD and NE). No formal statistical analyses are planned. BOR will be presented based on the BICR data and also the investigator recorded data.

ORR will be analysed using logistic regression adjusted by the stratification factors. If the number of responses in the individual stratum are too small for a meaningful analysis (less than 5 responses per stratum), a pre-specified strategy to account for such a situation, will be applied. Further details will be documented in the Statistical Analysis Plan.. Results of the analysis will be presented in terms of an odds ratio (olaparib vs. chemotherapy) together with its associated 95% CI and 2-sided p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model). CIs will be profile likelihood CIs (e.g. using the option 'LRCI' in SAS procedure GENMOD). ORR will be analysed for the BICR data and also the investigator recorded data.

A response of CR or PR will not require confirmation due to the randomized controlled study design as per the RECIST guidelines.

10.5.2.2 Subgroup analysis for the primary endpoint (ORR)

Subgroup analyses will be conducted comparing ORR between treatments. The purpose of the subgroup analyses is to assess the consistency of treatment effect across potential or expected prognostic factors. If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 patients in a subgroup), the relationship between that subgroup and ORR will not be formally analysed. In this case, only descriptive summaries will be provided.

The following subgroups of the full analysis set will be analysed for ORR

Stratification factors

- •Selected study chemotherapy (paclitaxel/topotecan/pegylated liposomal doxorubicin/gemcitabine)
- •Number of prior chemotherapy regimens received for ovarian cancer (2 or 3 vs. 4 or more)
- •Time to disease progression on last platinum based chemotherapy received prior to randomisation (6 – 12 months / > 12 months)
- Additional subgroups of interest include:

- BRCA mutation type, e.g. BRCA1, BRCA2 or BRCA1/2 (both)

- •Age at randomisation (<65 vs. ≥65)
- •Region
- •Race
- •ECOG performance status at baseline (0, 1, or 2)

Other baseline variables may also be assessed if there is clinical justification.

For each subgroup, the ORs (olaparib: physician's choice of chemotherapy) and associated CIs will be calculated from an adjusted logistic regression model, provided there are enough responses for a meaningful analysis. The model will include stratification factors. No adjustment to the significance level for testing will be made since all these subgroup analyses will be considered exploratory and may only be supportive of the primary analysis of ORR.

The ORR analysis will be repeated excluding any patients who did not have a gBRCA mutation status confirmed by the Myriad test. The response rate in each treatment arm will be presented. No formal statistical analyses will be conducted.

10.5.2.3 Sensitivity analyses for the primary endpoint (ORR)

(a) Ascertainment bias

A stratified logistic regression will be repeated using the programatically derived RECIST using investigator assessed ORR. The OR and 95% Confidence Interval will be presented.

If there is an important discrepancy between the primary analysis using BICR assessments and this sensitivity analysis using investigator assessments, then the proportion of patients with site but no central confirmation of objective response will be summarised.

Disagreements between investigator and central reviews of RECIST objective response will be presented for each treatment group. The summary will include the early discrepancy rate which is the frequency of central review declared responses before the investigator review as a proportion of all central review responses and the late discrepancy rate which is the frequency of central review declared responses after the investigator review as a proportion of all responses.

(b) Subjects with evaluable disease at baseline

As a sensitivity analysis to the primary ORR analysis, the analysis will be repeated including all patients with evaluable disease at baseline. This will include all patients in the Measurable Disease Analysis Set (MDAS) and patients with non-measurable disease at baseline, but presenting with non-target lesions at baseline. No formal statistical analyses will be conducted.

(c) Full Analysis Set

As a sensitivity analysis to the primary ORR analysis, the analysis will be repeated including all randomised patients. (All patients in the FAS). No formal statistical analyses will be conducted.

(d) Confirmed response

A sensitivity analysis of confirmed CR or PR will be conducted. A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue treatment without progression, receive a subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) and then respond will not be included as responders in the ORR (i.e. both visits contributing to a response must be prior to subsequent therapy for the patient to be considered as a responder).

In the case where a patient has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a responder. Similarly, if a patient has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

(e) Deviation bias (if meaningful to do)

As a sensitivity analysis to the primary endpoint of ORR, an analysis excluding patients with deviations that may affect the efficacy of the trial therapy will be performed if > 10% of patients:

• did not have the intended disease or indication or

• did not receive any randomised therapy

A stratified logistic regression will be repeated using the BICR RECIST data, using the same ties and stratification factors as described for the primary analysis of ORR. The OR and 95% CI will be presented.

10.5.3 Analysis of the secondary variable(s)

10.5.3.1 PFS analysis

PFS will be analysed using a log rank test stratified by the stratification factors.If the number of events in the individual stratum are too small for a meaningful analysis (less than 5 events per stratum), a pre-specified strategy to account for such a situation, will be applied. Further details will be documented in the Statistical Analysis Plan. The hazard ratio (HR) and

confidence interval will be estimated from the U and V statistics obtained directly from the LIFETEST model with inclusion of STRATA terms for the stratification variables, if applicable (and using the Breslow approach for handling ties).

The HR and its confidence interval will be estimated from the log-rank as follows (Berry et al 1991 and Sellke et al 1983)

HR = exp(U/V)

95% CI for HR = (exp{U/V – 1.96/ √V}, exp{U/V + 1.96/ √V})

Where $U = \sum_i (d_{1i} - e_{1i})$ is the log-rank test statistic (with d_{1i} and e_{1i} the observed and expected events in group 1) and √V the standard deviation of the log-rank test statistic as produced in the LIFETEST output.

The HR (olaparib vs. chemotherapy) together with its corresponding 95% confidence interval (CI) and p-value will be presented (a HR less than 1 will favour olaparib).

Any patients mis-stratified in the IVRS will be included in the stratified log rank test using the baseline data collected in the IVRS.

A Kaplan-Meier (KM) plot of PFS will be presented by treatment group. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST or death) will be provided along with median PFS for each treatment arm.

The assumption of proportionality will be assessed. Note that in the presence of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up. Proportionality will be tested firstly by producing plots of complementary log-log (event times) versus log (time) and, if these raise concerns, a time dependent covariate would be fitted to assess the extent to which this represents random variation.

The PFS analysis will be based on the programmatically derived PFS based on BICR assessments, and using all scans regardless of whether they were scheduled or not.

The estimated PFS rates at 6 months and 12 months will be summarised (using the KM curve) and presented by treatment group.

The number of patients prematurely censored will be summarised by treatment arm 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 one scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date.

As patients will be randomised, imbalances in demographic factors between the treatment groups are not anticipated. However if any imbalances should occur, the HR and associated confidence interval calculated from a Cox Proportional Hazards model containing treatment, stratification variables and these additional demographic variables, may be reported.

10.5.3.1.1 Subgroup analysis for PFS

Subgroup analyses will be conducted comparing PFS between treatments. The purpose of the subgroup analyses is to assess the consistency of treatment effect across potential or expected prognostic factors. If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup and PFS will not be formally analysed. In this case, only descriptive summaries will be provided.

The following subgroups of the full analysis set will be analysed for PFS

Stratification factors

- Selected study chemotherapy (paclitaxel/topotecan/pegylated liposomal doxorubicin/gemcitabine)
- Number of prior chemotherapy regimens received for ovarian cancer (2 or 3 vs. 4 or more)
- Time to disease progression on last platinum based chemotherapy received prior to randomisation (6 – 12 months / > 12 months)

Additional subgroups of interest include:

- Measurable versus non-measurable disease
- *BRCA* mutation type, e.g. *BRCA1, BRCA2* or *BRCA1/2* (both)
- Age at randomisation (<65 vs. ≥65)
- Region
- Race
- ECOG performance status at baseline (0, 1, or 2)

Other baseline variables may also be assessed if there is clinical justification.

For each subgroup, the HRs (olaparib: physician's choice of chemotherapy) and associated CIs will be calculated from a Cox proportional hazards model (ties = Efron) that contains the treatment term, factor and treatment-by-factor interaction term. The treatment effect HRs for each treatment comparison along with their confidence intervals will be obtained for each level of the subgroup from this single model. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI from the overall population (using the primary analysis).

No adjustment to the significance level for testing of subgroups will be made since all these subgroup analyses will be considered exploratory and may only be supportive of the primary analysis of PFS.

The presence of quantitative interactions will be assessed by means of an overall global interaction test. This will be performed in the overall population by comparing the fit of a Cox proportional hazards model including treatment, all covariates (stratification factors), and all covariate-by-treatment interaction terms, with one that excludes the interaction terms and will be assessed at the 2-sided 10% significance level. If the fit of the model is not significantly improved then it will be concluded that overall the treatment effect is consistent across the subgroups.

If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

Any quantitative interactions identified using this procedure will then be tested to rule out any qualitative interaction using the approach Gail and Simon 1985.

The PFS analysis will be repeated excluding any patients who did not have a gBRCA mutation status confirmed by the Myriad test. A Kaplan-Meier (KM) plot of PFS will be presented by treatment group. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST or death) will be provided along with median PFS for each treatment arm. No formal statistical analyses will be conducted.

10.5.3.1.2 Sensitivity analyses for PFS

Sensitivity analyses will be performed to assess the possible presence of time-assessment bias (i.e., differential assessment times between treatment groups).

Summary statistics for the number of weeks between the time of progression and the last evaluable RECIST assessment prior to progression will be presented for each treatment group.

(a) Evaluation-Time bias

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment will be analysed using a stratified log rank test, as described for the primary PFS analysis. This approach has been shown to be robust to even highly asymmetric assessment schedules (Sun and Chen 2010). This approach will use the BICR RECIST assessments.

(b) Attrition bias

Attrition bias will be assessed by repeating the primary PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following two, or more, non-evaluable tumour assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

Additionally a Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary PFS analysis is reversed will be presented.

(c) Ascertainment bias

A stratified log-rank test will be repeated using the programmatically derived RECIST using investigator assessed PFS. The HR and 95% Confidence Interval will be presented.

If there is an important discrepancy between the primary analysis using BICR assessments and this sensitivity analysis using investigator assessments, then the proportion of patients with site but no central confirmation of progression will be summarised. The approach of imputing an event at the next visit in the central review analysis may help inform the most likely HR value, but only if an important discrepancy exists.

Disagreements between investigator and central reviews of RECIST progression will be presented for each treatment group. The summary will include the early discrepancy rate which is the frequency of central review declared progressions before the investigator review as a proportion of all central review progressions and the late discrepancy rate which is the frequency of central review declared progressions after the investigator review as a proportion of all discrepancies.

(d) Deviation bias (if meaningful to do)

As a sensitivity analysis to the primary PFS analysis, an analysis excluding patients with deviations that may affect the efficacy of the trial therapy will be performed if > 10% of patients:

- did not have the intended disease or indication or
- did not receive any randomised therapy

A stratified log-rank test will be repeated using the BICR RECIST data, using the same ties and stratification factors as described for the primary analysis of PFS. The HR and 95% CI will be presented.

10.5.3.2 Analysis of PFS2 endpoint

An initial PFS2 analysis will be performed at the same time as the primary analysis of ORR and will use the same methodology and model as the PFS analysis. If the number of events in the individual stratum are too small for a meaningful analysis (less than 5 events per stratum), a pre-specified strategy to account for such a situation, will be applied. Further details will be documented in the Statistical Analysis Plan. If there are less than 20 events, descriptive summaries will be provided only. A further analysis of PFS2 will be performed when the OS data are approximately 60% mature only if both ORR and PFS are statistically significant based on the primary analysis and the null hypotheses for PFS2 and/or OS are not rejected at the time of the primary analysis.

The analysis of PFS2 will be repeated excluding any patients who did not have a *gBRCA* mutation status confirmed by the Myriad test. The same methodology and model will be used and the HR and associated 95% CI from a Cox Proportional Hazards model will be reported.

10.5.3.3 Analysis of OS endpoint

OS data will be analysed at the time of the primary analysis of ORR and will use the same methodology and model as the PFS analysis If the number of deaths in the individual stratum are too small for a meaningful analysis (less than 5 deaths per stratum), a pre-specified strategy to account for such a situation, will be applied. Further details will be documented in the Statistical Analysis Plan. If there are less than 20 deaths, descriptive summaries will be provided only. A further analysis of OS will be performed when the OS data are approximately 60% mature, only if both ORR and PFS are statistically significant based on the primary analysis and the null hypotheses for PFS2 and/or OS are not rejected at the time of the primary analysis.

A Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary OS is reversed will be generated.

The analysis of OS will be repeated excluding any patients who did not have a *gBRCA* mutation status confirmed by the Myriad test. The same methodology and model will be used and the HR and associated 95% CI from a Cox Proportional Hazards model will be reported.

10.5.3.4 Time to earliest progression by RECIST 1.1 or CA-125 or death

Time to earliest progression by RECIST 1.1, CA-125 or death will be performed at the same time as the primary analysis and will use the same methodology and model as the PFS endpoint.

The analysis of time to earliest progression by RECIST 1.1, CA-125 or death will be repeated excluding any patients who did not have a *gBRCA* mutation status confirmed by the Myriad test. The same methodology and model will be used and the HR and associated 95% CI from a Cox Proportional Hazards model will be reported.

No multiplicity adjustment will be applied as this is viewed as a supportive endpoint (to PFS).

10.5.3.5 Time to first subsequent chemotherapy or death (TFST)

As a supportive analysis for PFS, time to start of first subsequent chemotherapy or death will be analysed using the same methodology and model as that used for the primary analysis of PFS. The HR for the treatment effect together with its 95% CI will be presented. In addition, a Kaplan Meier plot of time to start of first subsequent chemotherapy or death will be presented by treatment arm. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint.

The analysis of TFST will be repeated excluding any patients who did not have a *gBRCA* mutation status confirmed by the Myriad test. The same methodology and model will be used and the HR and associated 95% CI from a Cox Proportional Hazards model will be reported.

A summary table of first subsequent therapies by treatment arm will be provided.

10.5.3.6 Time to study treatment discontinuation (TDT)

Similarly as a supportive analysis for PFS, time to study treatment discontinuation or death will be analysed using the same methodology and model as that used for the primary analysis of PFS. The HR for the treatment effect together with its 95% CI will be presented. In addition, a Kaplan Meier plot of time to study treatment discontinuation or death will be presented by treatment arm. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint.

The analysis of TDT will be repeated excluding any patients who did not have a *gBRCA* mutation status confirmed by the Myriad test. The same methodology and model will be used and the HR and associated 95% CI from a Cox Proportional Hazards model will be reported.

10.5.3.7 Time to second subsequent chemotherapy or death (TSST)

As a supportive analysis for PFS2, time to start of second subsequent chemotherapy or death will be analysed using the same methodology and model as that used to analyse PFS2. The HR for the treatment effect together with its 95% CI will be presented. In addition, a Kaplan Meier plot of time to start of second subsequent chemotherapy or death will be presented by treatment arm. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint.

The analysis of TSST will be repeated excluding any patients who did not have a *gBRCA* mutation status confirmed by the Myriad test. The same methodology and model will be used and the HR and associated 95% CI from a Cox Proportional Hazards model will be reported.

A summary table of second subsequent therapies by treatment arm will be provided.

10.5.3.8 Duration of Response (DoR) and CA-125 response

Descriptive data will be provided for the DoR in responding patients (i.e. median duration of response and 95% CIs) by treatment arm, including the associated Kaplan-Meier curves (without any formal comparison of treatment arms or p-value attached).

In addition, the number and percentage of patients reporting a CA-125 response, an objective RECIST 1.1 response and both a CA-125 and/or objective RECIST response will be tabulated.

10.5.3.9 Time to response (TTR)

The TTR will be summarised (i.e. number of patients [%] based upon the number of responders for each cohort) by the scheduled assessment timepoint that the response was first observed. Additionally, descriptive summary statistics (i.e. minimum, maximum, median, Q1 and Q3) will also be presented.

10.5.3.10 FACT-O

The analysis population for HRQoL data will be the subset of the FAS.

Change from baseline in TOI score will be regarded as the primary analysis of the FACT-O questionnaire and will be analysed using a mixed model for repeated measures (MMRM) analysis of the change from baseline in TOI score for each visit. The primary analysis will be to compare the average treatment effect from the point of randomisation for the first 8 months (which will include visit data obtained at baseline, weeks 4, 8, 16 and 32). Other timepoints and the study discontinuation visit and the safety follow-up visit will be excluded from this analysis but may be included on supportive summaries and graphical displays as appropriate.

The MMRM model will include patient, treatment, visit and treatment by visit interaction as explanatory variables and the baseline TOI score as a covariate. Treatment, visit and treatment by visit interaction will be fixed effects in the model; patient will be included as a random effect. The treatment by visit interaction will remain in the model regardless of significance. Calculation of a suitable adjusted mean estimate will be detailed in the SAP that will estimate the average treatment effect over visits which gives each visit equal weight. The adjusted mean estimates and corresponding 95% confidence intervals will be presented for the overall treatment comparison and by visit for each treatment group.

Descriptive statistics and graphs will be reported for the TOI by visits as well as change in these scores from baseline. These will also be reported for the physical well-being (PWB), social well being (SWB), emotional well being (EWB), functional well-being (FWB) and the ovarian cancer subscale (Additional Concerns) domains.

Summary tables of Trial Outcome Index (TOI) best change rates will be provided. TOI improvement rate will be analysed using a logistic regression model and using the same covariates as used in the PFS analyses. If there are <5 patients with a response of improved no analysis will be performed. If there are <50 patients with a response in a treatment group a Fisher's exact test will be considered and mid p-values used. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood 95% confidence intervals and p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

Summary tables of best change rates and analysis of improvement rates will be performed for the physical well being (PWB), social well being (SWB), emotional well being (EWB),

functional well being (FWB) and the ovarian cancer subscale (Additional Concerns) domains for both change from baseline and improvement rates. P-values will not be calculated for these supportive analyses.

10.5.4 Analysis of Exploratory Endpoints

10.5.4.1 Cancer Therapy Satisfaction Questionnaire (CTSQ-16)

The treatment satisfaction score (as measured by the Satisfaction with Therapy scale of the CTSQ-16) and patient-reported feelings measured by the 'feelings about side-effects' domain of the Cancer Therapy Satisfaction Questionnaire (CTSQ-16) will be summarised by treatment arm.

10.5.4.2 Analysis of Healthcare Resource Use

An exploratory health economic analysis of resource use will be estimated, including descriptive statistics relating frequency of hospitalisations and hospital admission, type of attendance, length of stay and procedures undertaken, and the primary symptom/reason for the attendance.

10.5.4.3 Health State Utility – EQ-5D-5L

Descriptive statistics will be reported for EQ-5D-5L health state utility values and the visual analogue score by visit, as well as change in these scores from baseline. Further details of the exploratory analysis will be outlined in the statistical analysis plan (SAP).

The scores for each of the EQ-5D-5L health state utility values and visual analogue will be summarised in terms of mean changes from baseline at each post-baseline assessment (with n, standard deviation, min, max presented). If less than 50% of the items in one health state are missing, the mean scores for the completed items will be used for imputation. If 50% or more of the items in one health state are missing, that subscale will be treated as missing.

10.5.4.4 Patient Global Impression of Change – PGIC

Descriptive statistics will be reported for PGIC for week 24 and discontintuation. Further details of the exploratory analysis will be outlined in the statistical analysis plan (SAP).

10.5.4.5 Impact of switching to PARP inhibitors (or other potentially active investigational agents) on Overall Survival Analyses

Exploratory analyses of OS adjusting for impact of subsequent PARP inhibitor trial or treatment may be performed if a sufficient proportion of patients receive the therapies of interest. Methods such as Rank Preserving Structural Failure Time (RPSFT) (Robins et al 1991), Inverse Probability of Censoring Weighting (IPCW) (Robins 1993) and other methods in development will be explored. The decision to adjust and final choice of methods will be based on a blinded review of the data and the plausibility of the underlying assumptions. Baseline and time-dependent characteristics will be explored, and summaries of baseline characteristics will be summarised for patients receiving physician's choice of chemotherapy, splitting between those that have and haven't received a PARP inhibitor at the time of the

analyses. Further detail will be provided in the SAP and Payer Analysis Plan. These analyses are intended to support reimbursement appraisals.

10.5.4.6 Exploratory translational science endpoints

Full statistical methods for 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.

BRCA status will be summarised for all patients based on the central Myriad test result. This will highlight any patients with a negative *BRCA* result from the central test.

10.5.5 Interim analysis

No formal statistical interim analyses for ORR or PFS are planned for this trial. The data cut-off for primary analysis will occur in January 2019 or at a minimum of 6 months after LSI, whichever is sooner. PFS2 and OS will be analysed at the time of the primary analysis. An additional PFS2 and OS analysis will only be conducted with further follow up (~60% OS events) if both ORR and PFS are statistically significant based on the primary analysis and the null hypotheses for PFS2 and/or OS are not rejected at the time of the primary analysis.

This study will use an external Independent Data Monitoring Committee (IDMC) to perform interim reviews of accumulating study safety data. This committee will be composed of therapeutic area experts and a statistician, who are not employed by AZ, and do not have any major conflict of interest. Following the review, the IDMC will recommend whether the study should continue unchanged, be terminated, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca. The report will only include the recommendation and any potential protocol amendments and it will not contain any unblinded information or reference to the confidential considerations of the committee to have led to their recommendation. A separate IDMC charter will be developed which will contain any details of the IDMC members and clearly define the responsibilities of the IDMC.

In addition to the periodic review of safety data by an IDMC, the safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with the Patient Safety Department. Issues identified will be addressed; this could involve, for instance, amendments to the study protocol and letters to investigators.

11 STUDY AND DATA MANAGEMENT

11.1 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 ePROs system(s) utilised.

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

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

11.2 Monitoring of the study

During the study, a designated 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 designated 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.

11.2.1 Source data

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

11.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of 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 or designated CRO and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

11.2.3 Archiving of study documents

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

11.3 Study timetable and end of study

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

At the time of study analysis completion (final analysis per CSP or any interim analysis resulting in decision of no more data collection required) number of patients can still be on study drug. These patients are to continue treatment as long as beneficial in investigator opinion. At this time point, the clinical study database will close to new data. Patients are, however, permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from treatment with olaparib.

Patients' treatment can be continued:

- Within current study

- Within special rollover or safety extension study if available

- Within drug supply program (commercial supply or other compassionate use program) if applicable

In case of treatment continuation **within current study**:

Assessment will revert to standard of care at particular site.

There would be no more data collection except SAE reporting. Clinical Study Database would be closed.

Paper form process would be used for SAE reporting. All SAEs, overdoses and pregnancies would be reported until 30 days after last dose.

Study drug would be supplied to sites manually outside of IXRS system. Drug dispensation and reconciliation will be handled by site on each patient's visit.

Study would be opened until last patient treated. Final Last Subject Last visit will be defined as last patient's treatment discontinuation.

In case of **special Rollover or Safety Extension Study** available

for patients remaining in this study after analysis finalized, they can be transferred to such umbrella protocol.

Rollover or Safety Extension study has to be fully approved by Regulatory and Ethics bodies applicable for patient's site.

Such study would ensure proper treatment continuation with visits assessment per its protocol.

Visits assessments will be covering minimum needed for safety oversight. Can cover as well assessments found as required for long term use analysis.

Any patient that would be proposed to move to such study, would be given with new Informed Consent Form.

If **study drug would be approved on market** for use in disease under study indication

patients may be discontinued and switched to marketed product. Drug supply options can be available depending on the country and would be proposed to patient when found as best way to continue treatment by both AZ and investigator.

For patients who do continue to receive treatment beyond the time of this data cut-off, Investigators will continue to report all SAEs to AstraZeneca Patient Safety until 30 days after study treatment is discontinued, in accordance with Section 6.4. 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. Additionally as stated in Section 6.3, any SAE or non-serious adverse event that is ongoing at the time of this data cut-off, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

The study is expected to start in Q4 2014 and to end by Q1 2021, or when the study transition to PART (post-analysis treatment) will be finalized.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the

entire study prematurely if concerns for safety arise within this study or in any other study with olaparib.

11.4 **Data management**

Data management will be performed by [redacted].

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 WHODRUG. All coding will be performed by the Medical Coding Team at [redacted]

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

The data will be validated as defined in the Study Plans. 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.

Site staff will enter PRO booklet data into the WBDC system.

12 ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

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

12.2 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.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law. The exception to the above is the results of the Myriad *gBRCA* test, this will be made available to the investigator and patient.

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, a Study Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

12.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca 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 Ethics Committee 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, the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca or designated CRO 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 Principal Investigator 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 or designated CRO will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

12.4 **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, including any information on the mandatory and optional sampling e.g. *BRCA* testing and tumour biopsies.
- 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.

12.5 **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 12.3.

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

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

12.6 **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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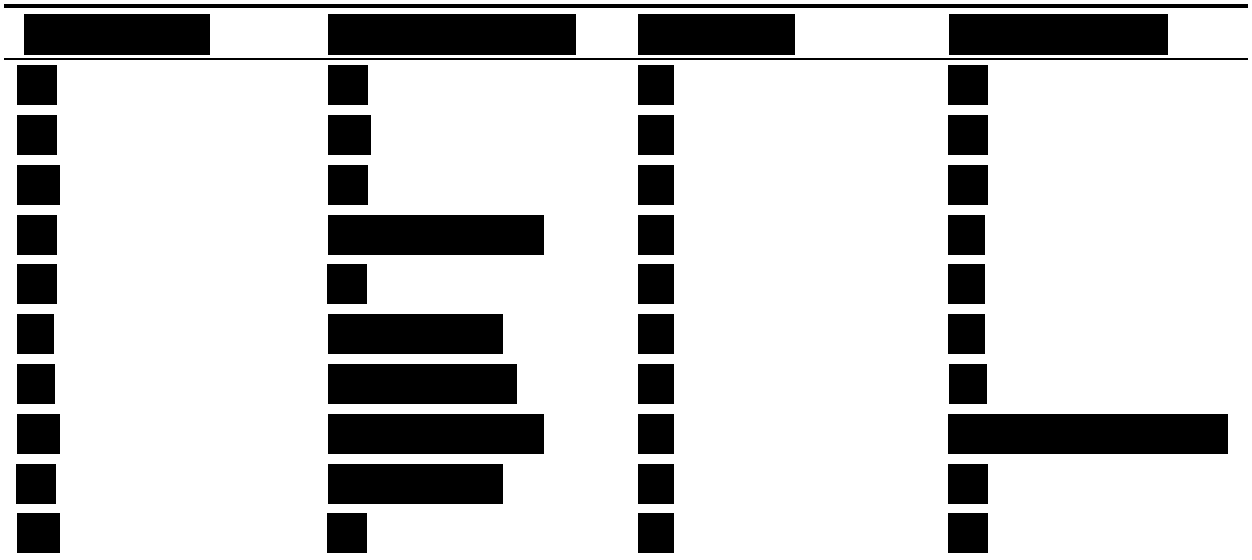

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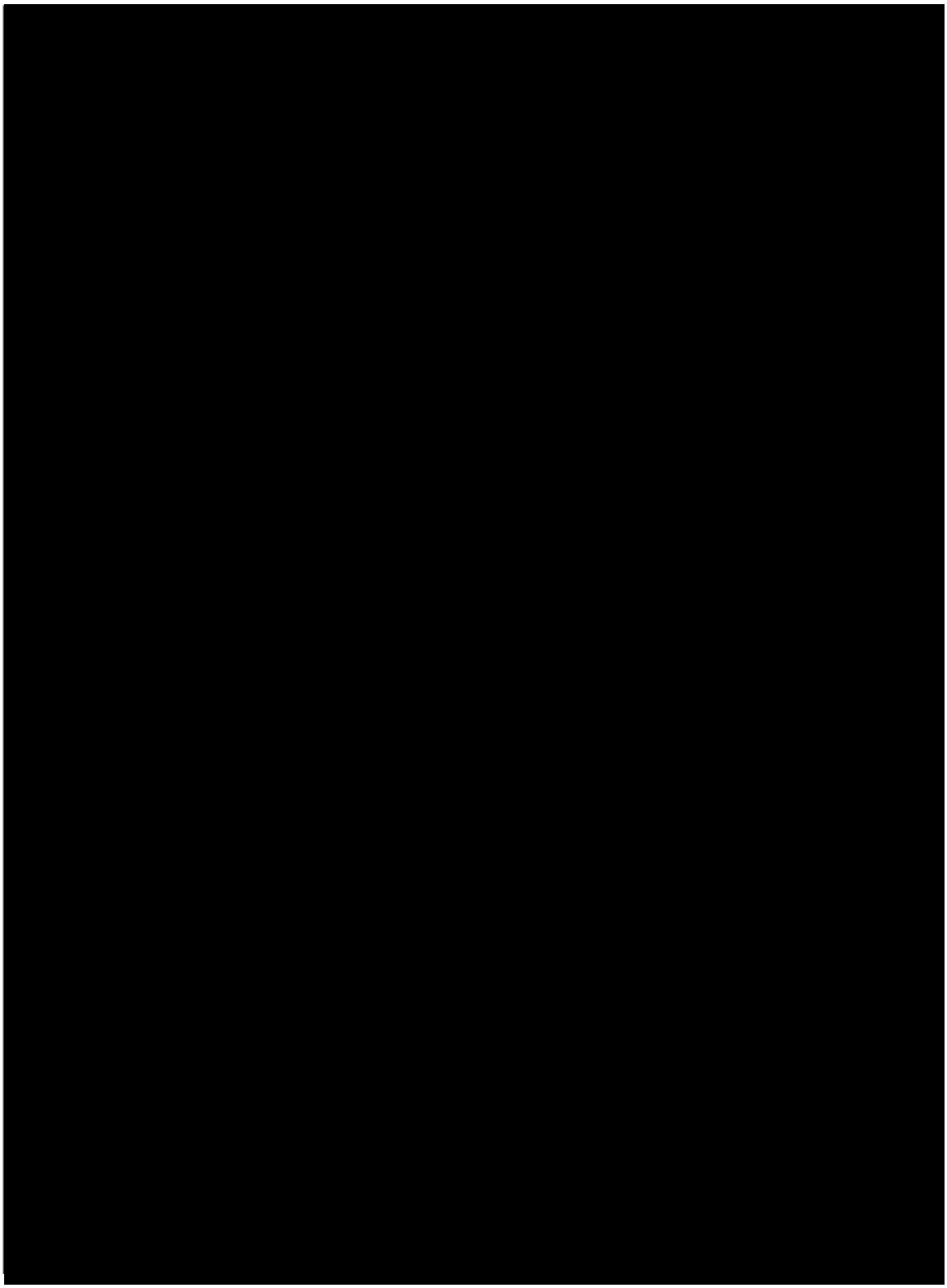

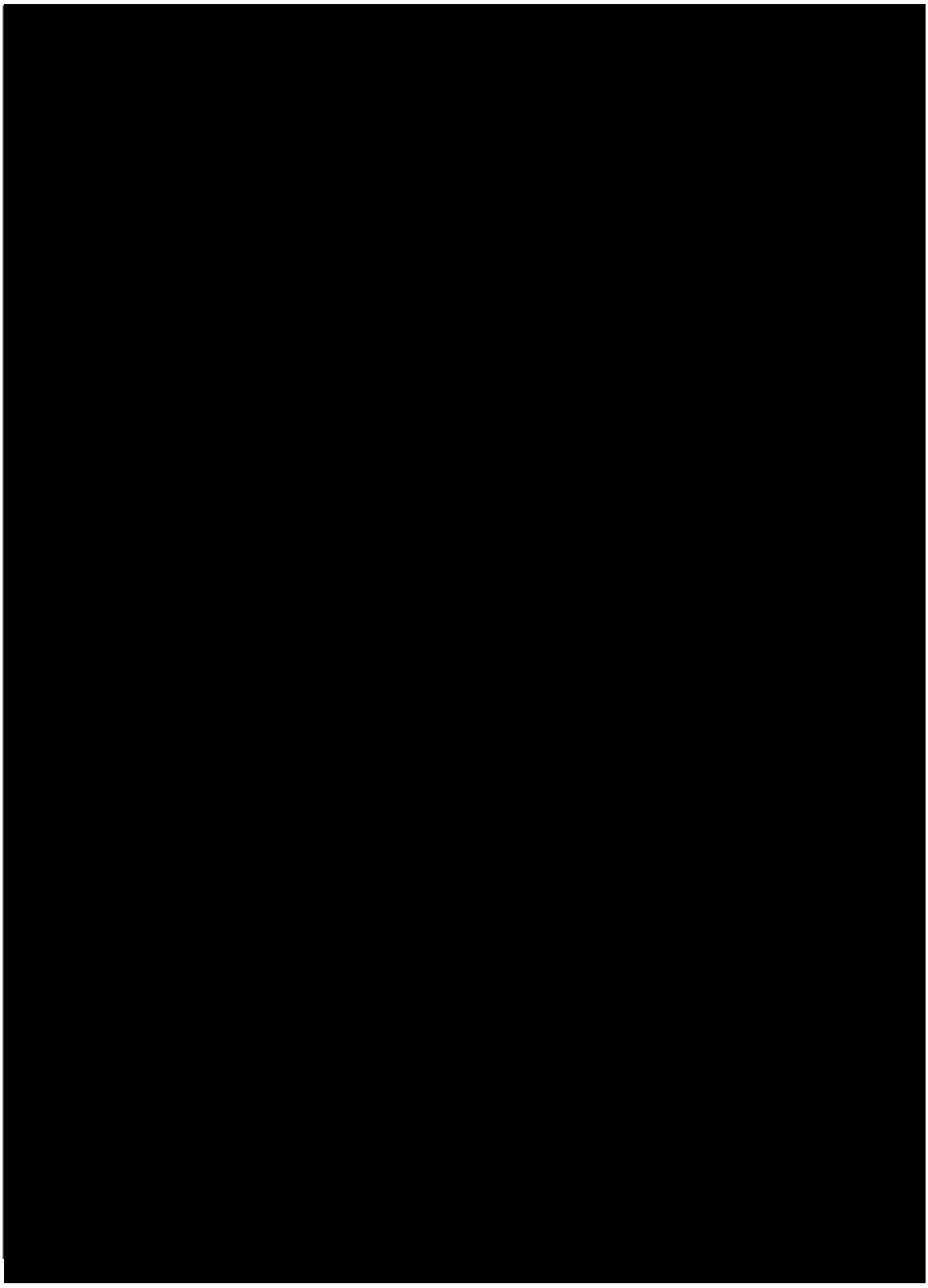

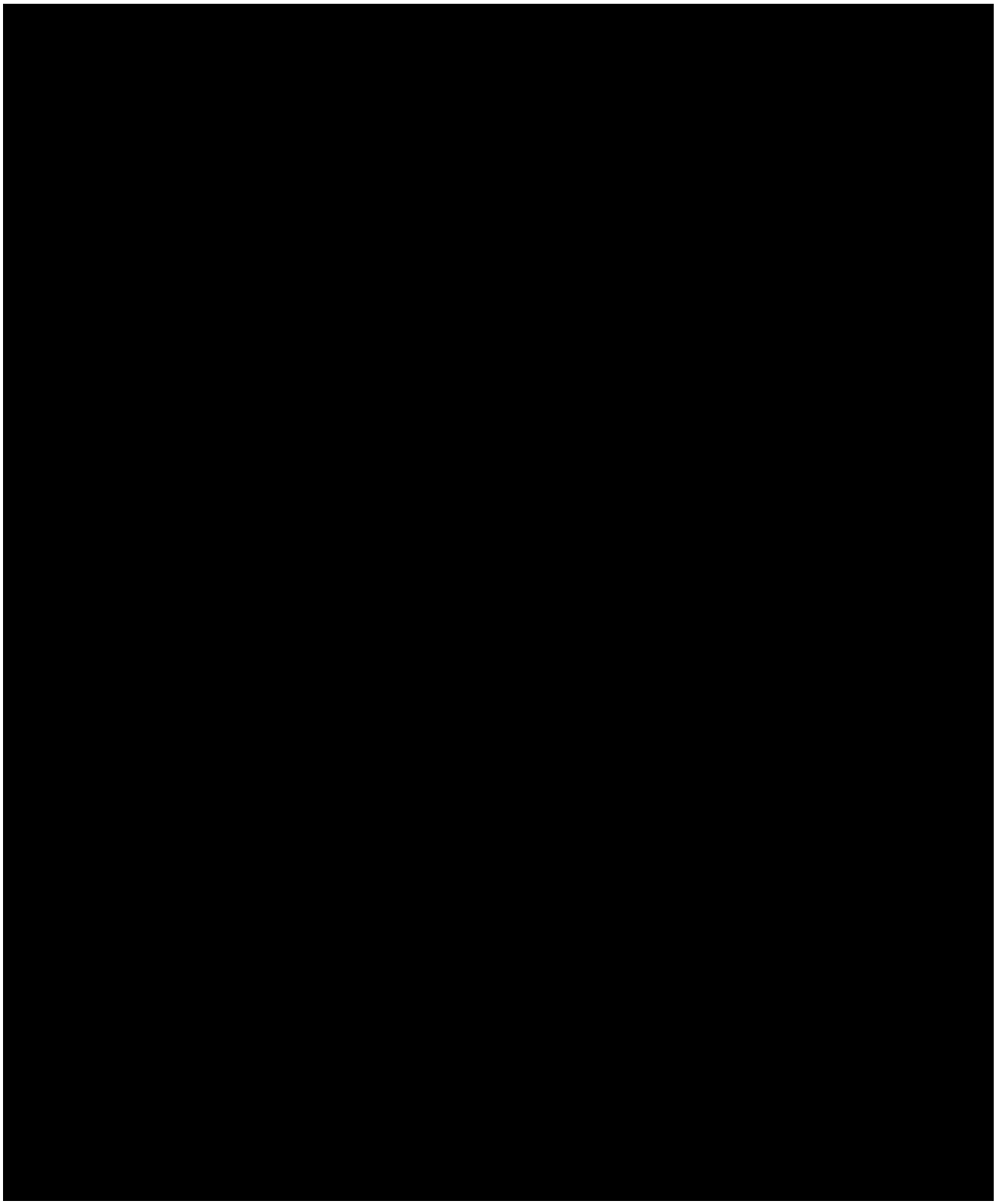

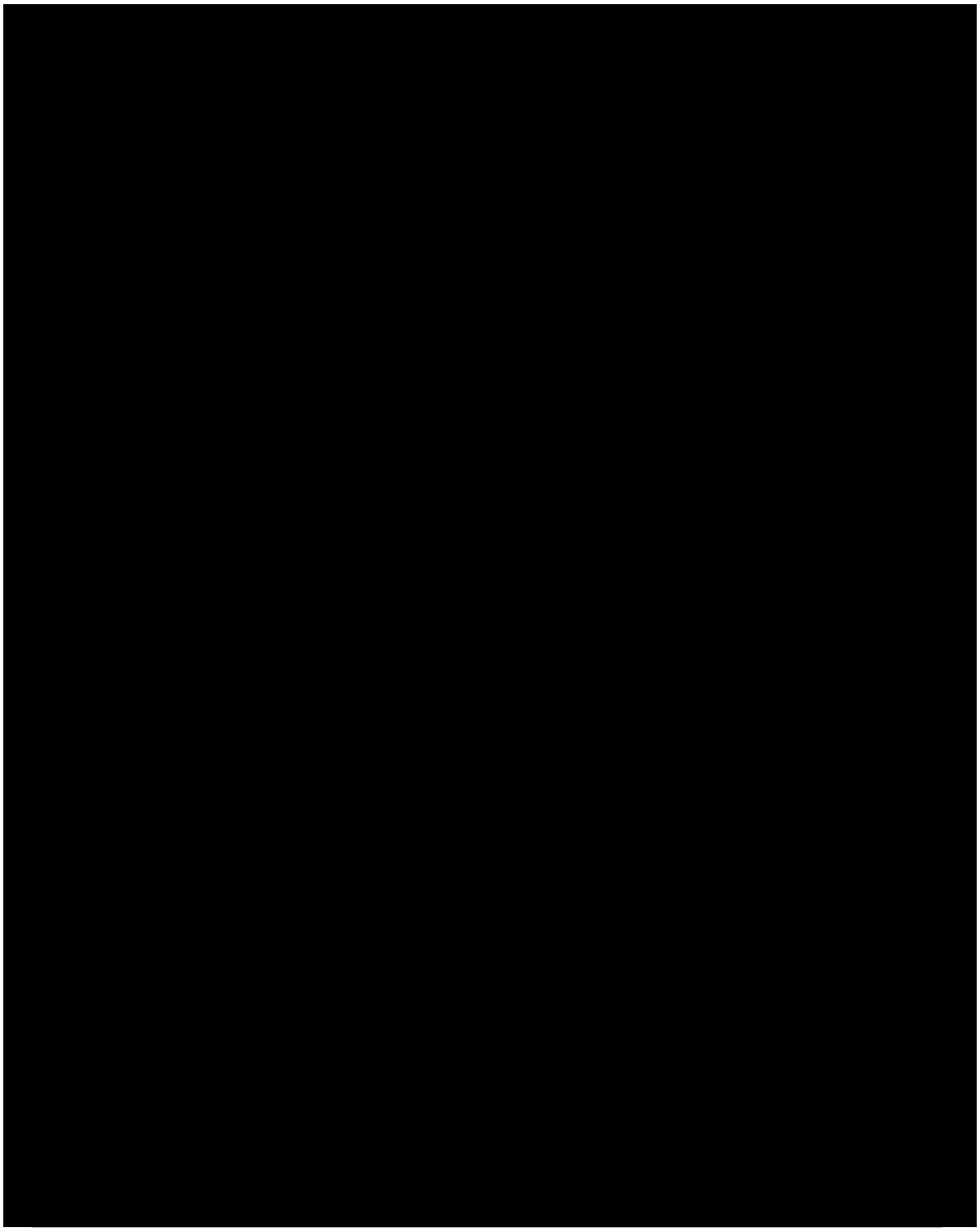

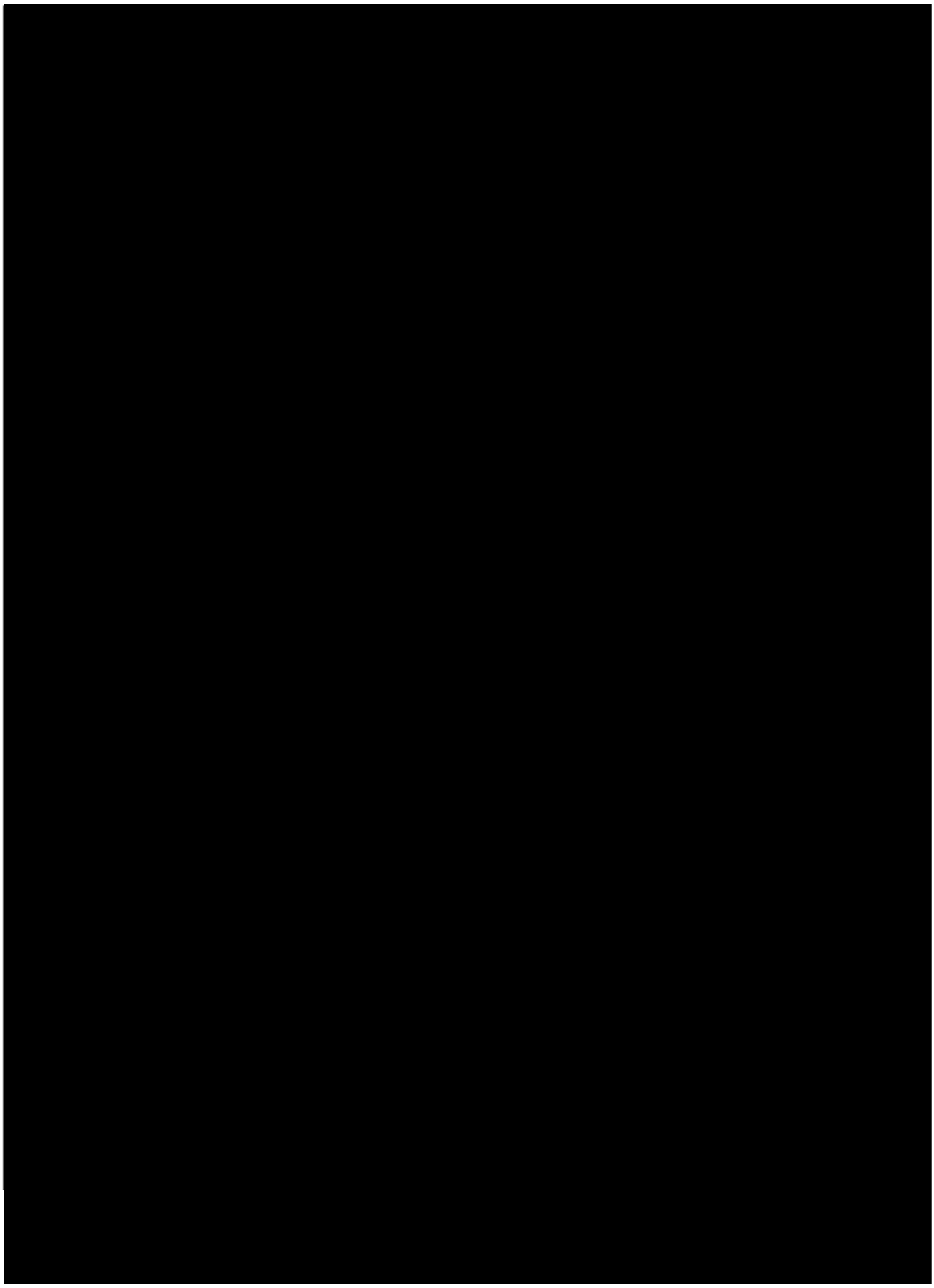

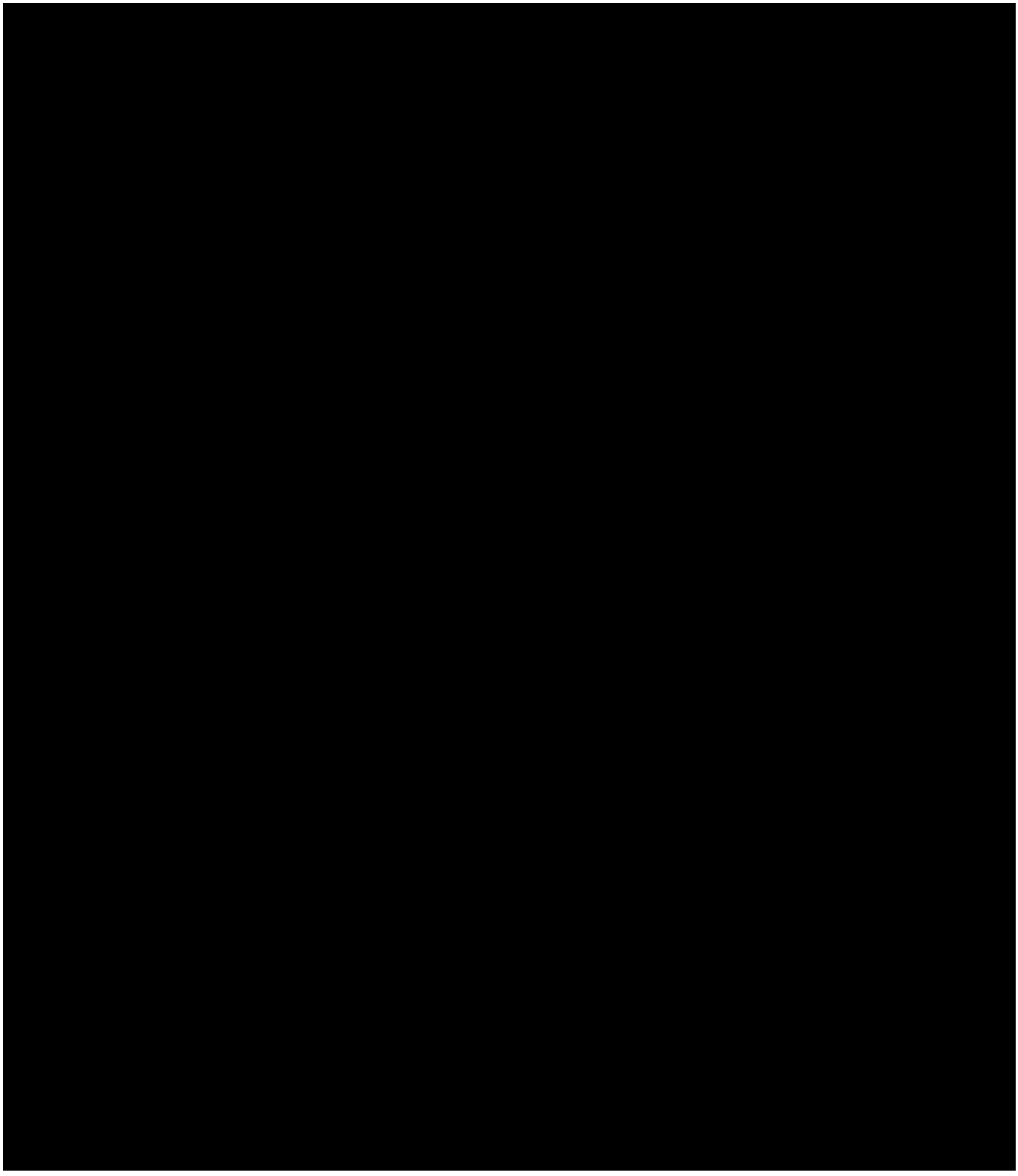

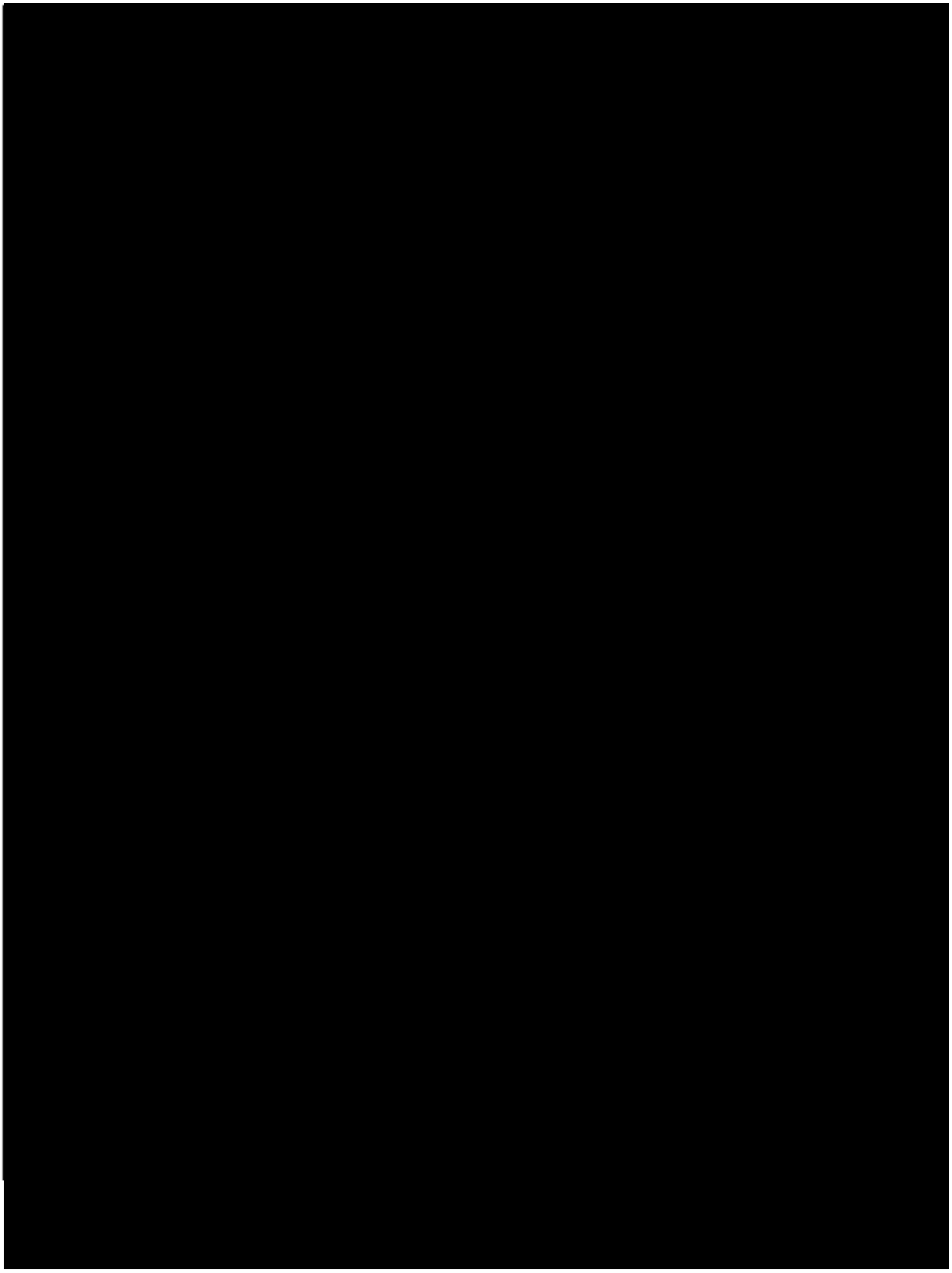

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21-Dec-2017 10:47 GMT+0000	[redacted]	Clinical Operations Approval
21-Dec-2017 15:08 GMT+0000	[redacted]	Medical Monitor Approval
21-Dec-2017 16:15 GMT+0000	[redacted]	Clinical Approval

Notes: (1) Document details as stored in [redacted] an AstraZeneca document management system.