AstraZeneca

Statistical Analysis Plan

Study Code	D0816C00012
Edition Number	5.0
Date	19 February 2020

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

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PPD

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AC	Additional Concerns
AE	Adverse event
AML	Acute Myeloid Leukaemia
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BP	Blood Pressure
BRCA	Breast cancer susceptibility gene (in accordance with scientific convention, gene and mutation is italicised whereas protein is not italicised)
*BRCA*m	g*BRCA* and/or s*BRCA* mutated
CA-125	Cancer antigen 125
CI	Confidence Interval
CR	Complete Response
CSP	Clinical Study Protocol
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating Tumour DNA
DCO	Date Cut-Off
DNA	Deoxyribonucleic Acid
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EU	European Union
EWB	Emotional well-being
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-O	Functional Assessment of Cancer Therapy-Ovarian
FAS	Full Analysis Set
FLIE	Functional Living Index-Emesis
CCI [redacted]	
FWB	Functional well-being
g*BRCA*	germline *BRCA*

Abbreviation or special term	Explanation
g*BRCA*m	germline *BRCA* mutated
GCIG	Gynaecological Cancer Inter Group
HRQoL	Health-Related Quality of Life
HRR	Homologous Recombination Repair
HRRm	Qualifying mutation in the tumour of any of 15 genes involved in DNA homologous recombination repair
IP	Investigational Product
KM	Kaplan-Meir
LOF	Loss of Function
LOH	Loss of Heterozygosity
MedDRA	Medical Dictionary for Regulatory Activities
MDS	Myelodysplastic Syndrome
MRI	Magnetic Resonance Imaging
NE	Not evaluable
NED	No evidence of disease
NTL	Non-target Lesion
OAEs	Other Significant Adverse Events
OS	Overall Survival
PARP	Poly-adenosine 5'diphosphoribose (ADP) Polymerase
PD	Progression of Disease
PFI	Progression Free Interval
PFS	Progression Free Survival
PFS2	Second Progression Free Survival
p.o.	Administered by mouth
PR	Partial Response
PRO	Patient Reported Outcome
PT	Preferred Term
PWB	Physical well-being
QoL	Quality of Life
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious adverse event

Abbreviation or special term	Explanation
s*BRCA*m	Somatic tumour *BRCA* mutated (mutation detected in the tumour but not in the germline)
SD	Stable Disease
SOC	System Organ Class
SWB	Social/family well-being
TDT	Time to Discontinuation of Treatment
TFST	Time to First Subsequent Treatment
TL	Target Lesion
TOI	Trial Outcome Index
TSST	Time to Second Subsequent Treatment
ULN	Upper Limit of Normal
ULRR	Upper Limit of Response Range
WBDC	Web Based Data Capture
WHODrug	World Health Organization Drug

AMENDMENT HISTORY

Category: Change refers to	Date	Brief description of change	In line with CSP? Y (version) / No /NA	Rationale
Other	23 March 2016 (V2.0)	Updated in accordance with protocol edition 2, 22 December 2015. Key changes in the CSP were a clarification of the populations of interest; a reduction in sample size required; and additional secondary endpoints related to QoL and safety.	Y (Ed 2)	To limit the enrolment of patients previously diagnosed with germline *BRCA* mutated disease and ensure that at least 50 patients with somatic *BRCA* mutated disease will be enrolled. To specify that, following consultancy with the Committee for Human Medicines Products (CHMP): The assessment of effectiveness of olaparib in the cohort of patients with somatic *BRCA* mutated disease, based on progression-free survival, has become a primary endpoint. Quality of life objectives have become secondary objectives.
Other	3 November 2016 (V3.0)	Updated in accordance with protocol edition 3, 22 July 2016; addition of an HRR exploratory cohort	Y (Ed 3)	The real world clinical effectiveness and safety of olaparib maintenance therapy will be described for this exploratory HRRm cohort.
Other	31 May 2019 (V4.0)	Updated in preparation for protocol, edition 4, 22 March 2019, which was not subsequently approved.	Y (Ed 4)	Protocol V4 was intended to allow the study to stop after primary analysis.

Category: Change refers to	Date	Brief description of change	In line with CSP? Y (version) / No /NA	Rationale
Other	19 February 2020 (V5.0)	Updated to bring text in line with current Oncology standards; updated text around protocol deviations to be more specific; clarification that the exploratory endpoint around Loss of Heterozygosity will be reported as an addendum to the primary CSR; addition of summary tables for common Olaparib AEs based on grouped preferred terms; clarification of subgroup on penultimate platinum chemotherapy; the primary objective is no longer referenced as co-primary to avoid confusion with the interpretation of study outcomes. The study does not test formal statistical hypotheses. As such, the study does not require the implementation of formal statistical procedures to protect from reporting false positive results	Y (Ed 3)	To clarify text around analysis procedures.

1. STUDY DETAILS

1.1 Study Objectives

1.1.1 Primary Objectives

The primary objectives are listed below:

- To assess the real-world clinical effectiveness of olaparib maintenance monotherapy by investigator assessed progression free survival (PFS) according to modified Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 in patients with somatic *BRCA* mutated (s*BRCA*m) ovarian cancer.

- To assess the real-world clinical effectiveness of olaparib maintenance monotherapy by investigator assessed PFS according to RECIST 1.1 in patients with *BRCA* mutated (*BRCA*m) ovarian cancer.

1.1.2 Secondary Objectives

The secondary objectives are listed below:

- To assess the real-world clinical effectiveness of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer, by assessment of:

  (a) Overall survival (OS)

  (b) Time to investigator-assessed second progression (PFS2), or death

- To assess the real-world clinical effectiveness of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer, by assessment of

  (a) Time to first subsequent therapy or death (TFST)

  (b) Time to second subsequent therapy or death (TSST)

  (c) Time to olaparib discontinuation or death (TDT)

- To assess and describe the quality of life (QoL) of patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer.

- To describe the nature and patterns of adverse events (AEs) of nausea and vomiting and their impact on QoL in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer. To describe nausea/vomiting toxicity management patterns used in routine clinical practice.

1.1.3 Safety Objective

- To assess the safety and tolerability of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer.

1.1.4 Exploratory Objectives

- To describe the longer-term safety of olaparib monotherapy, including follow up for Myelodysplastic Syndrome (MDS)/ Acute Myeloid Leukaemia (AML)/ and New primary malignancies (other than MDS/AML).

- To correlate the incidence of side effects and QoL according to age and the presence of comorbidities.

- To describe the clinical effectiveness of (response to) subsequent line of treatment and correlating it with the progression-free interval (PFI) (artificial prolongation of PFI through olaparib).

- To describe the efficacy of olaparib according to the previous therapy, with or without bevacizumab, and according to the PFI (recurrence during or after the end of bevacizumab maintenance).

- To describe the activity of olaparib according to the germline mutational status (*BRCA*1 vs *BRCA*2), and to the presence of family history (yes vs no).

- To describe the kinetic of CA-125 progression according to Gynaecological Cancer Inter Group (GCIG) criteria and its correlation with disease progression by RECIST 1.1 guidelines during olaparib therapy.

- To measure loss of heterozygosity (LOH) for the *BRCA*1 and *BRCA*2 genes in tumour samples and explore any potential association with efficacy*.

- To describe the real-world clinical effectiveness and safety of olaparib maintenance monotherapy in patients with *BRCA*-independent homologous recombination repair gene mutated (HRRm) ovarian cancer, by the following (for definition of HRRm cohort, please refer to Section 1.2):

  (a) Investigator assessed PFS according to RECIST 1.1

  (b) OS

  (c) Safety and tolerability.

- Potential exploratory research into frequency, nature and predictive value of HRR gene mutations, including *BRCA*1 and *BRCA*2, may be performed on the optional collected and stored tumour samples available at study entry or tumour biopsy samples collected during the course of the study. These could include studying

resistance mechanisms to olaparib, future exploratory research into factors that may influence development of cancer and/or response to study treatment. To collect and store DNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response to study treatment and/or susceptibility to disease (optional)*.

- To explore the feasibility of reliably measuring s*BRCA*m and HRRm from circulating tumour DNA (ctDNA)**

*This exploratory analysis will be reported as an addendum to the primary clinical study report (CSR).

**This exploratory analysis will not be reported in the (CSR). They will be reported separately.

1.2 Study design

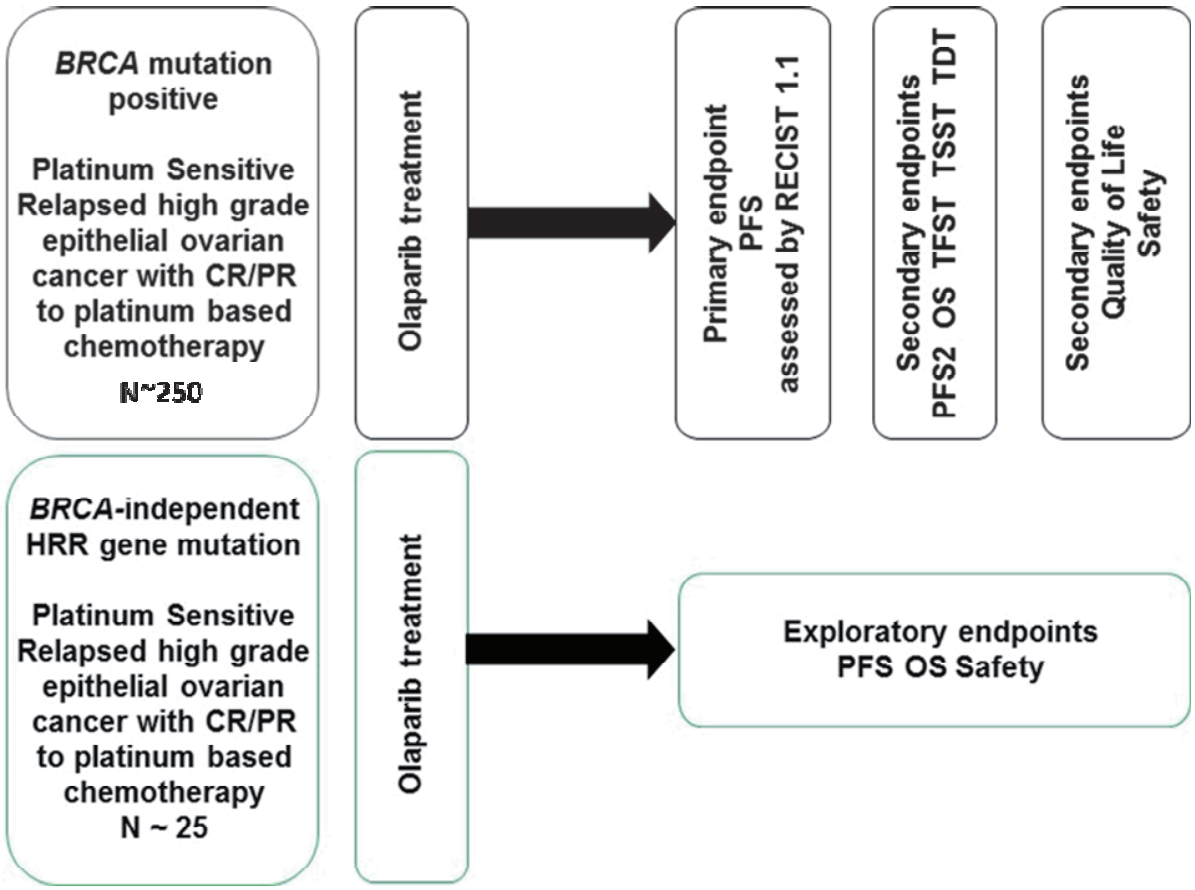
This is a prospective, open-label, single arm, multi-centre study to assess the real-world clinical effectiveness and safety of olaparib maintenance monotherapy will be conducted in patients with platinum-sensitive relapsed *BRCAm* (germline and/or somatic) high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response [CR] or partial response [PR]) to platinum-based chemotherapy.

BRCA mutations are documented germline or somatic mutations in *BRCA*1 or *BRCA*2 that are predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function).

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

The study flow chart is presented in Figure 1.

Figure 1 Study Flow Chart



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

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

The schedule of assessments is found in Tables 1, 2, and 3 of the clinical study protocol.

1.3 Number of patients

Patients enrolled with sBRCAm disease

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

All BRCAm patients

The sample size of approximately 250 patients is driven by the need to have at least 50 patients with s*BRCA*m disease, and to help understand patterns of olaparib use in routine clinical practice with the capsule formulation and across various subgroups. Assuming a median PFS value of 11.2 months and a data cut off at approximately 60% maturity then with approximately 23 months of non-linear recruitment, ~60% maturity is expected to occur approximately 32 months after FSI.

Patients enrolled with HRRm disease

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

2. ANALYSIS SETS

2.1 Definition of analysis sets

Table 1 gives a summary of outcome variables and analysis populations.

Table 1 Summary of Endpoints, Analysis Populations and Patient Groups

Endpoints	Populations	Patient Groups
Primary endpoints		
PFS in patients with *BRCA*m disease	Full Analysis Set	*BRCA*m*
PFS in patients with s*BRCA*m disease	Full Analysis Set	s*BRCA*
Secondary endpoints		
OS, PFS2, TFST, TSST, TDT	Full Analysis Set	*BRCA*m* and s*BRCA*m
QoL: FLIE, FACT-O, FACIT-F, ORZORA Qol (additional ovarian cancer items)	Full Analysis Set	*BRCA*m* and s*BRCA*m
Safety endpoints		
AEs, SAEs, Lab results, vital signs.	Safety Analysis Set	*BRCA*m*, s*BRCA*m, and HRRm^
Exploratory endpoints		
Incidences of MDS/AML, new primary malignancies, pneumonitis.	Safety Analysis Set	*BRCA*m*, s*BRCA*m, and HRRm^
PFI with olaparib.	Full Analysis Set	*BRCA*m
PFI for penultimate platinum therapy.	Full Analysis Set	*BRCA*m
CA-125 progression.	Full Analysis Set	*BRCA*m
PFS and OS in patients with *BRCA*m independent HRRm disease	Full Analysis Set	HRRm^
Demographics and Baseline characteristics	Full Analysis Set	*BRCA*m*, s*BRCA*m and HRRm^

*g*BRCA*m patient group will also be presented for completeness
HRRm^=HRRm excluding *BRCA*1 and *BRCA*2
TFST: time to first subsequent therapy or death; TSST: time to second subsequent therapy or death; TDT: time to olaparib discontinuation or death; PFS2: Investigator assessed second progression; OS: Overall survival; PFI: Progression-free interval.

*BRCA*m, g*BRCA*m, s*BRCA*, and HRRm^ subgroups will be calculated based on:

Mutation	Conditions
g*BRCA*m	• g*BRCA*m=”Yes” for patients with BLOOD mutation: o If patient is from protocol edition = 1, the patient should show all these 3 characteristics Loss of function mutation = “Yes” AND *BRCA* mutation type = “*BRCA*1” or “*BRCA*2” or “both” AND *BRCA* mutation category = “Deleterious mutation” or “Genetic variant, suspected deleterious” o If patient is from protocol edition > 1, the patient should show all these 5 characteristics *BRCA* Tested = “current (central)” AND *BRCA* Laboratory = “Myriad Genetics Lab” AND Loss of function mutation = “Yes” AND *BRCA* mutation type = “*BRCA*1” or “*BRCA*2” or “both” AND *BRCA* mutation category = “Deleterious mutation” or “Genetic variant, suspected deleterious” • Otherwise g*BRCA*m=”No”
s*BRCA*m	• s*BRCA*m=”Yes” for patient with TUMOR mutation: o If patient is from protocol edition = 1, the patient should show all these 5 characteristics g*BRCA* ≠ (“Not tested” and missing) AND g*BRCA*m=”No” AND Loss of function mutation = “Yes” AND *BRCA* mutation type = “*BRCA*1” or “*BRCA*2” or “both” AND *BRCA* mutation category = “Deleterious mutation” or “Genetic variant, suspected deleterious” o If patient is from protocol edition > 1, the patient should show all these 7 characteristics g*BRCA* ≠ (“Not tested” and missing) AND g*BRCA*m=”No” AND *BRCA* Tested = “current (central)” AND *BRCA* Laboratory = “Myriad Genetics Lab” AND Loss of function mutation = “Yes” AND *BRCA* mutation type = “*BRCA*1” or “*BRCA*2” or “both” AND *BRCA* mutation category = “Deleterious mutation” or “Genetic variant, suspected deleterious” • Otherwise s*BRCA*m=”No”
*BRCA*m	• *BRCA*m=”Yes” for patient with g*BRCA*m=”Yes” OR s*BRCA*m=”Yes” • Otherwise *BRCA*m=”No”
HRRm^	• HRRm^=”Yes” for patients with HRRm status= “mutated” AND g*BRCA*m=”No” AND s*BRCA*m=”No” • Otherwise HRRm^=”No”

2.1.1 Full analysis set

The full analysis set includes all patients who have been assigned olaparib (all enrolled patients as an intention to treat analysis set). Patients are considered enrolled once it is confirmed that they meet all eligibility criteria and the request has been made by the Investigator for the provision of study treatment for that patient. Where a patient does not meet all the eligibility criteria but is enrolled in error, she will still be a part of the FAS. All efficacy analyses will be based on the Full Analysis Set (FAS).

Patient Reported Outcomes (PRO) (FLIE, HRQoL (FACT-O, FACIT-Fatigue, and a set of new ovarian cancer items) will be based on the FAS with additional exclusion criteria for each PRO analysis independently, excluding:

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

2.1.2 Safety analysis set

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

2.2 Violations and deviations

The following general categories will be considered important protocol deviations to be included in the CSR. These will be listed and discussed in the CSR as appropriate:

- Patients entered but who did not receive study treatment (Deviation 1).
- Patients who deviate from key entry criteria per the Clinical Study Protocol (CSP) (inclusion criteria 3, 4 and 5, exclusion criteria 4, 5, 6, 7 and 8) (Deviation 2).
- Baseline RECIST scan > 42 days before first dose of study treatment (Deviation 3).
- No baseline RECIST 1.1 assessment on or before date of first dose of study treatment (Deviation 4).
- Received prohibited concomitant medications (including other anti-cancer agents) (Deviation 5). Please refer to the CSP section 7.7 for those medications that are detailed as being ‘excluded’ from permitted use during the study. This will be used as a guiding principle for the physician review of all medications prior to database lock.

The important protocol deviations will be listed and summarised using the FAS group. Deviation 1 will lead to exclusion from the safety analysis set. None of the other deviations will lead to patients being excluded from the analysis sets described in section 2.1.

The final classification of deviations will be made based on regular meetings with AstraZeneca.

3. PRIMARY AND SECONDARY ENDPOINTS

3.1 Derivation of RECIST visit response

The primary PFS endpoint will be based on investigator-assessment according to RECIST 1.1 guidelines.

Where it is available, the RECIST tumour response data will be used to determine each subject's visit response according to RECIST version 1.1 (Eisenhauer et al 2009). It will also be used to determine if and when a subject has progressed in accordance with RECIST 1.1 and also their best objective response.

Baseline radiological tumour assessments are to be performed no more than 28 days prior to starting olaparib and as close as possible to the start of olaparib. Tumour assessments are then performed every 12 weeks (±1 week) relative to date of enrolment, until disease progression as determined by the investigator.

At each visit, an overall visit response will be determined programmatically - using the information from target lesions (TL), non-target lesions (NTL) and new lesions. RECIST 1.1 outcomes will be calculated using a computer program.

3.1.1 Target lesions (TLs)

Measurable disease is defined as having at least one measurable lesion which is ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI). A subject can have a maximum of 5 measurable lesions recorded at baseline and these are referred to as target lesions (TLs). If more than one baseline scan is recorded, then measurements from the one that is closest to enrolment will be used to define the baseline sum of TLs.

Note: For patients who do not have measurable disease at entry (i.e. no TLs), evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions (see section 3.1.3 for further details). If a patient does not have measurable disease at baseline, then the TL visit response will be not applicable (NA).

Table 2 TL visit responses

Visit Reponses	Description
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of target lesions and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not evaluable (NE)	Only relevant in certain situations (i.e. if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response.
Not applicable (NA)	No target lesions are recorded at baseline.

Rounding of TL data:

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to 1 decimal place before assigning a target lesion response. For example, 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data:

For a visit to be evaluable then all target lesion measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded
- A NTL visit response of PD is recorded
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5mm, from nadir even assuming the non-recorded TLs have disappeared

Lymph nodes

For lymph nodes, if the size reduces to < 10mm then these are considered non-pathological. However, a size will still be given and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10mm and all other TLs are 0mm then although the sum may be >0mm the calculation of TL response should be over-written as a CR.

TL Visit responses subsequent to CR

A CR response can only be followed by CR, PD or NE. If a CR has occurred, then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met i.e. if a lymph node LD increases by 20% but remains < 10mm.

- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to NE irrespective of whether when referencing the sum of TL diameters, the criteria for PD is also met.

- Step 3: If not all lesions meet the CR criteria (i.e. a pathological lymph node selected as TL has short axis > 10mm or the reappearance of previously disappeared lesion) or a new lesion appears, then response will be set to PD.

- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR.

TL too big to measure

If a target lesion becomes too big to measure this should be indicated in the database and a size ('x') above which it cannot be accurately measured should be recorded. If using a value of x in the calculation of target lesion response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team. It is expected that a visit response of PD will remain in the vast majority of cases.

TL too small to measure

If a target lesion becomes too small to measure a value of 5mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered a smaller value that can be reliably measured. If a target lesion response of PD results (at a subsequent visit), then this will be reviewed by the study team.

Irradiated lesions/lesion intervention

Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolization), should be handled in the following way and once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumours:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.

- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and scale up as described below as long as there remain ≤ 1/3 of the TLs with missing measurements. If the scaling results in a visit response of PD then the subject would be assigned a TL response of PD.

- Step 3: If after both steps PD has not been assigned, then a scaled sum of diameters will be calculated (as long as ≤ 1/3 TLs have missing measurements), treating the lesion with intervention as missing, and PR or SD then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or <10mm for lymph nodes) and the lesions that have been subject to intervention also has a value of 0 recorded. If scaling up is not appropriate due to too few non-missing measurements, then the visit response will be set to NE.

At subsequent visits the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up (as per step 2 above).

Scaling (applicable only for irradiated lesions/lesion intervention)

If ≤ 1/3 of the target lesion measurements are missing (because of an intervention) then the results will be scaled up (based on the sizes at the nadir visit) to give an estimated sum of diameters and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements.

Example of scaling

Lesion	Longest diameter at nadir visit	Longest diameter at follow-up visit
1	7.2	7.1
2	6.7	6.4
3	4.3	4.0
4	8.6	8.5
5	2.5	Intervention
Sum	**29.3**	**26**

Lesion 5 is missing at the follow-up visit.

The sum of lesions 1-4 at the follow-up is 26 cm. The sum of the corresponding lesions at nadir visit is 26.8 cm.

Scale up as follows to give an estimated TL sum of 28.4cm:

$$\frac{26}{26.8} \times 29.3 = 28.4cm$$

CR will not be allowed as a TL response for visits where there is missing data. Only PR, SD or PD (or NE) could be assigned as the TL visit response in these cases. However, for visits with ≤1/3 lesion assessments not recorded, the scaled up sum of TLs diameters will be included when defining the nadir value for the assessment of progression.

Lesions that split in two

If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If two target lesions merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0cm.

Change in method of assessment of target lesions

CT, MRI and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination only used in special cases (see study protocol for more information of tumour assessment of this study). If a change in method of assessment occurs between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (e.g. CT changes to clinical examination or vice versa), any affected lesions should be treated as missing.

3.1.2 Non-target lesions (NTLs) and new lesions

Non-target lesion response will be derived based on the Investigator's overall assessment of NTLs as follows:

Progressive disease:	Unequivocal progression of existing NTLs, which may be due to an important progression in one lesion only or in several lesions
Complete response:	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10mm short axis).
Non-CR/Non-PD:	Persistence of one or more NTLs with no evidence of progression.
Not evaluable:	Only relevant when one or some of the NTLs have not been assessed and in the Investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit.
Not applicable:	Only relevant if there are no NTLs at baseline

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present and should be treated as NE in the derivation of overall visit response.

3.1.3 Overall visit response

Table 3 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 3 Overall Visit Response

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

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

For patients with no disease at baseline (i.e. no TLs and no NTLs), evaluation of overall visit responses will be based on absence/presence of new lesions. If no TLs and no NTLs are recorded at a visit, both the TL and NTL visit response will be recorded as NA and the overall visit response will be no evidence of disease (NED). If a new lesion is observed, then the overall visit response will be PD.

3.2 Primary endpoint

3.2.1 Progression Free Survival (PFS)

PFS is defined as the time from the date of enrolment until the date of objective radiological disease progression (assessed via RECIST 1.1), or death (by any cause in absence of disease progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to disease progression (i.e. date of PFS event or censoring – date of enrolment + 1). Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable efficacy assessment. However, if the patient progresses or dies immediately after two or more missed visits, the patient will be censored at the time of the latest evaluable assessment prior to the two missed visits (Note: NE visit is not considered as missed visit).

Given the scheduled visit assessment scheme (tumour assessment every 12 weeks), two missing visits will equate to 26 weeks since the previous RECIST 1.1 assessment, allowing for early and late visits. If the patient has no evaluable visits or does not have a baseline

assessment, they will be censored at day 1 unless they die within two visits of baseline (25 weeks allowing for visit window).

The date of the first progression will be programmatically determined from investigator assessed data. 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:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a patient for PFS the patient will be censored at the latest of the 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.

3.3 Secondary endpoints

All time to event endpoints (OS, PFS2, TFST, TSST, and TDT) will be described as for PFS in the subset of patients with s*BRCA*m disease, and for all patients with *BRCA*m disease.

3.3.1 Overall Survival (OS)

OS is defined as the time from the date of enrolment until death due to any cause regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy (i.e. date of death or censoring – date of enrolment + 1). 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 (SUR_DAT, recorded within the SURVIVE module of the electronic case report form (eCRF)).

Assessments for survival should be made every 12 weeks following disease progression. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. Survival data will be collected up to the time of the final analysis. Survival calls will be performed in the week following the date of data cut off (DCO) for the analysis and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO.

For the ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the analysis, survival information should be obtained by the site personnel by contacting the patient, 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.

In the absence of survival calls being made, it may be necessary to use all relevant eCRF fields to determine the last recorded date on which the patient was known to be alive. The last date for each individual patient is defined as the latest among the following dates recorded on the eCRFs:

- AE start and stop dates
- Admission and discharge dates of hospitalization
- Study treatment date
- End of treatment date
- Laboratory test dates
- Date of vital signs
- Disease assessment dates on RECIST eCRF
- Start and stop dates of alternative anticancer treatment
- Date last known alive on survival status eCRF
- End of study date

3.3.2 Time to second progression or death (PFS2)

Time from enrolment to second progression is defined as the time from the date of enrolment to the earliest of the progression event subsequent to that used for the primary variable PFS or death (by any cause in the absence of progression). Patients whose progression event for PFS was death will have this counted as a progression event for PFS2 also. The date of second progression will be recorded by the investigator and defined according to local standard clinical practice and may involve any of the following: objective radiological, symptomatic, CA-125 progression or death. The date of the PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded on the eCRF. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, i.e. censored at the last assessment for progression date if the patient has not had a second progression or death.

Patients should be assessed every 12 weeks for a second progression (using the patient's status at first progression as the reference for assessment of second progression).

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

As a supportive summary to PFS, time to start of first subsequent anti-cancer therapy or death (TFST) will be assessed. Time to first subsequent anti-cancer therapy or death is defined as the time from the date of enrolment to the earlier of first subsequent anti-cancer therapy start date, or death date (i.e. date of first subsequent cancer therapy/death or censoring – date of enrolment + 1). Any patient not known to have had a further subsequent therapy or death will be censored at the last date that the patient was known not to have received a first subsequent anti-cancer therapy. If a patient terminated the study for reason other than death before first subsequent therapy, these patients will be censored at the earliest of their last known to be alive and termination dates (study discontinuation date).

3.3.4 Time to second subsequent anti-cancer therapy or death (TSST)

As a supportive summary to PFS2, time to start of second subsequent anti-cancer therapy or death (TSST) will be assessed. Time to second subsequent anti-cancer therapy or death is defined as the time from the date of enrolment to the earlier of the date of second subsequent anti-cancer therapy start date, or death date (i.e. date of second subsequent cancer therapy/death or censoring – date of enrolment + 1). Any patient not known to have had a second subsequent anti-cancer therapy or death will be censored at the last date the patient was known not to have received second subsequent anti-cancer therapy. If a patient terminated the study for reason other than death before second subsequent therapy, these patients will be censored at the earliest of their last known to be alive and termination dates (study discontinuation date).

3.3.5 Time to study treatment discontinuation or death (TDT)

Time to olaparib discontinuation or death (TDT) is defined as the time from the date of enrolment to the earlier of the date of study treatment discontinuation or death (earliest of [date of death; date of discontinuation of olaparib] or date of censoring – date of enrolment + 1). 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.

3.3.6 QoL endpoints

3.3.6.1 Patient Reported Outcomes (PROs)

The following Patient Reported Outcomes instruments (PROs) will be administered in this study: Functional Assessment of Cancer Therapy-Ovarian (FACT-O), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, the ORZORA QoL Additional Items Questionnaire (a set of newly developed ovarian cancer items) and Functional Living Index-Emesis (FLIE). Each is described below.

Administration of PRO questionnaires

Paper questionnaires were expected to be collected from the patient at baseline, at day 29, then every 12 weeks (+/- 7 days) for 24 months or up to the data cut off for the final analysis, whichever comes first. However, these were more frequently collected than expected, every 4

weeks, and the additional PRO questionnaires will also be presented in the tables. In addition, the FLIE questionnaire will be administered to the patient weekly in the first month from starting the study treatment in person or over the phone. In addition, PRO questionnaires will be collected at the discontinuation of study treatment visit and 30 days post last dose. Patients who had disease progression will complete the questionnaires during the 12 weekly survival follow ups either in person or over the phone. PRO questionnaires will be provided to patients and they will complete them on paper and site staff will enter information directly into the eCRF.

Evaluable patients for each PRO questionnaire

PRO analyses (FLIE, FACT-O. FACIT-Fatigue, ORZORA QoL Additional Items Questionnaire) will be based on the FAS. However, additional exclusion criteria will be considered for each PRO analysis separately:

- The subject does not have any evaluable baseline data
- The subject does not have any evaluable post-baseline data

Rules for Handling Missing Data of PRO questionnaires

Unless explicitly stated otherwise, missing data will not be imputed and data will be analysed and presented according to the following rule: 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 50% or more of the items are missing, that subscale also will be treated as missing. The reason (if available) 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 using other techniques such as simple/multiple imputation methods or statistical models.

Compliance of PRO questionnaires

Summary measures of overall compliance and compliance over time will be derived for the FACT-O, FACIT-Fatigue, and FLIE respectively. These will be based upon:

- Received questionnaire = a questionnaire that has been received and has a completion date and at least one individual item completed.
- Expected questionnaire = a questionnaire that is expected to be completed at a scheduled assessment time e.g. a questionnaire from a patient who has not withdrawn from the study at the scheduled assessment time but excluding patients in countries with no available translation. For patients that have progressed, the latest of progression and safety follow-up will be used to assess whether the patient is still under HRQoL follow-up at the specified assessment time. Date of study

discontinuation will be mapped to the nearest visit date to define the number of expected forms.

- Evaluable questionnaire = a questionnaire with a completion date and at least one subscale that is non-missing.

- Overall PRO compliance rate is defined as: Total number of evaluable questionnaires across all scheduled time points, divided by total number of questionnaires expected to be received across all scheduled time points multiplied by 100. Note: questionnaires completed at non-scheduled assessments will not contribute to this statistic.

- Overall patient compliance rate is defined as: Total number of patients with an evaluable baseline and at least one evaluable follow-up questionnaire (as defined above), divided by the total number of patients expected to have completed at least a baseline questionnaire multiplied by 100.

Compliance over time will be calculated separately for each visit, including baseline, as the number of patients with an evaluable questionnaire at the time point (as defined above), divided by number of patients still expected to complete questionnaires.

3.3.6.2 Functional Living Index-Emesis (FLIE)

The FLIE tool will be used to assess study treatment-induced nausea and vomiting. The FLIE consists of nine nausea-specific and nine vomiting-specific items that address the effect of nausea and vomiting on daily functioning following chemotherapy. The first item in each domain asks the patient to rate how much nausea and vomiting he or she has experienced in the past 3 days from day of FLIE completion. The remaining eight items covers different sections influencing the patient's quality of daily life (i.e., “recreation or leisure activities,” “make meal/do tasks,” “ability to enjoy meal,” “enjoy drinking fluids,” “see family/ friends,” “daily functioning,” “personal hardship,” “hardship on others”). For more details about FLIE questionnaire see Appendix 1.

- To derive nausea total score

Nausea total score = [(8-Q1) + (8-Q2) + Q3 + (8-Q4) + (8-Q5) + Q6 + (8-Q7) + (8-Q8) + (8-Q9)]*9/Number of items answered

Nausea total score range: 9-63

Nausea total score meaning: A higher score corresponds to a higher QoL or less impact on QoL

- To derive vomit total score

Vomit total score = [(8-Q10) + Q11 + (8-Q12) + (8-Q13) + (8-Q14) + Q15 + (8-Q16) + (8-Q17) + Q18]*9/Number of items answered

Vomit total score range: 9-63

Vomit total score meaning: A higher score corresponds to a higher QoL or less impact on QoL

- To derive FLIE total score

FLIE total score = Nausea total score + Vomit total score

FLIE total score range: 18-126

FLIE total score meaning: A higher score corresponds to a higher QoL or less impact on QoL

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

The FACT-O is composed of the following sub-scales: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB) as well as the additional concerns (AC) scales consisting of specific ovarian cancer (OCS) symptoms. For more details about FACT-O Scoring Guidelines see Appendix 2.

- To derive all subscales scores

Physical well-being (PWB) score = [(4-GP1) + (4-GP2) + (4- GP3) + (4- GP4) + (4- GP5) + (4- GP6) + (4- GP7)]*7/Number of items answered

PWB score range: 0-28

Social/family well-being (SWB) score = [GS1 + GS2 +GS3+ GS4 + GS5 + GS6 + GS7]*7/Number of items answered

SWB score range: 0-28

Emotional well-being (EWB) score = [(4-GE1) + GE2 + (4- GE3) + (4- GE4) + (4- GE5) + (4- GE6)]*6/Number of items answered

EWB score range: 0-24

Functional well-being (FWB) score = [GF1 + GF2 +GF3+ GF4 + GF5 + GF6 + GF7]*7/Number of items answered

FWB score range: 0-28

Ovarian Cancer Subscale (OCS) score (or Additional Concerns (AC) score) = [(4-O1) + (4-C2) + C3 + (4-O2) + (4-B5) + C6 + C7 + BMT5 + B9 + (4-O3) + BL4] * 11/Number of items answered

OCS score range: 0-44

OCS is a set of new ovarian cancer items added in FACT-O. Note that although the item BMT7 is included in the eCRF, this is not currently used to calculate OCS score (or AC score).

- To derive FACT-O total score

FACT-O Total score = PWB score + SWB score + EWB score + FWB score + OCS score

FACT-O Total score range: 0-152.

- To derive FACT-O Trial Outcome Index (TOI) score

FACT-O TOI score = PWB score + FWB score + OCS score

FACT-O TOI score range: 0-100.

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 threshold for a clinically important change is outlined below (Table 4):

Table 4 Health Related QoL

Score	Change from baseline*	Visit response
TOI	≥ +10	Improved[(1)]
	≤ -10	Worsened[(2)]
	Otherwise	No change[(3)]

[(1)]: Patients with baseline score > 90 cannot show improvement and will not be included in the denominator to evaluate the proportion of patients that have a response of Improved
[(2)]: Patients with baseline score < 10 cannot show worsening and will not be included in the denominator to evaluate the proportion of patients that have a response of Worsened
[(3)]: All patients with baseline score will be included in the denominator to evaluate the proportion of patients that have a response of No Change

Best Overall TOI improvement (in absence of starting any subsequent cancer therapy) will be defined as a change from baseline in the TOI of + 10 points or more sustained for at least 28 days, the denominator consisting of a subset of the FAS who have baseline TOI. It will be derived as the best symptom improvement response the patient achieved, based on evaluable QoL data collected from first olaparib dose up to the earliest of starting any subsequent cancer therapy or death. Therefore, at the conclusion of the trial, the following criteria will be used to assign a best overall score response based on the individual visit responses (Table 5).

Table 5 Health Related Quality of Life: Change rates - overall score

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

A TOI improvement rate (in the absence of subsequent cancer therapy) will be calculated as the proportion of all analysed patients with a best overall score response of improved. In the calculation of the proportion of patients that have a response of Improved, No Change or Worsened, the denominator used in the calculation will use the number evaluable for that individual TOI domain score at baseline (see notes of Table 4).

3.3.6.4 Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

The scores will be derived in accordance with the FACIT-Fatigue Scoring Guidelines. Final scores are the sum of the responses (0-52) where higher scores indicate better HRQoL (Yellen et al 1997). Changes in scores ≥ 3 points are considered to be clinically meaningful (Cella et al 2002. For more details about FACIT-F questionnaire see Appendix 3.

The calculation of the Fatigue score is presented below:

FACIT-F total score = [(4-HI7) + (4-HI12) + (4- An1) + (4- An2) + (4- An3) + (4- An4) + An5 + An7 + (4- An8) + (4- An12) + (4- An14) + (4- An15) + (4- An16)]*13 /Number of items answered.

3.3.6.5 ORZORA QoL Additional Items Questionnaire

In addition to FACT-O and FACIT-Fatigue, subjects will also complete the following set of newly developed ovarian cancer items: "I feel ill with low energy," "I am able to enjoy life and I am still interested in my hobbies and interests," "I am satisfied that my family understands my disease," "I feel I am able to meet the needs of my family," "I understand the need to take my medication and my treatment regimen," "My treatment has had significantly negative effects on my QoL," and "I feel like a normal woman" with the same recall period (7 days) and response options as in FACT-O. Finally, on a free text response scale, subjects will be asked to respond to the following question: "What are the 3 most significant issues you are struggling with, please list them starting with your worst first?". As no scoring guidelines exist for these new questions, the number and percentage of patients giving each response ("Not at all", "A little bit", "Somewhat", "Quite a bit", "Very much") will be summarised. For more details about ORZORA QoL Additional Items Questionnaire, see Appendix 4.

3.4 Exploratory endpoints

3.4.1 MDS/AML and New primary malignancies

Long term safety data of olaparib monotherapy, including follow up for Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukaemia (AML) and new primary malignancies, as well as pneumonitis, will be collected.

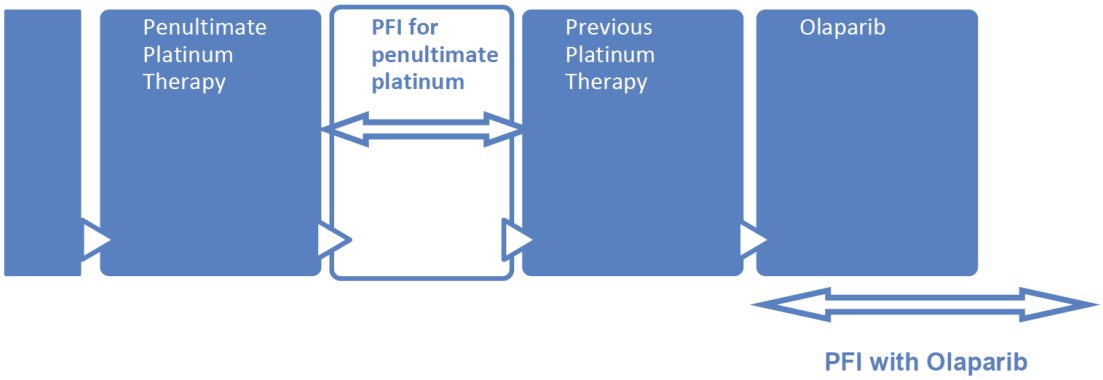
3.4.2 Side effects and Comorbidities

Side effects are recorded as AEs and comorbidities will be collected in medical history.

3.4.3 Progression Free Interval (PFI) with olaparib

The progression free interval (PFI) flow chart for penultimate platinum and for previous platinum therapy with olaparib is presented in Figure 2 below:

Figure 2 PFI Flow Chart



The analysis will be based on the investigator progression assessment. It is required that patients have clinical and objective radiological tumour assessments according to RECIST criteria.

PFI with olaparib is defined as the time from the last date of previous platinum chemotherapy dose until the date of progression on or after olaparib (PFS event date). Note that progression on or after olaparib will be date of objective radiological disease progression, regardless of whether the patient receives another anticancer therapy prior to disease progression. Patients who have died before progression on or after olaparib or have not progressed at the time of analysis will have their PFI measured up to the time of death (PFS event date) or PFS censoring date (see section 3.2.1 progression free survival (PFS) for more details of PFS event).

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

PFI with olaparib will be categorised as follows:

- PFI ≤ 6 months
- PFI between > 6 and ≤ 12 months
- PFI >12 months

Response to a subsequent line of therapy is defined as the best response to the first line of therapy post-olaparib. These data are collected in the eCRF as CR, PR, SD, PD, NE and not applicable.

3.4.4 Progression Free Interval (PFI) for penultimate platinum

PFI for penultimate platinum is defined as the time from the last date of penultimate platinum therapy (platinum therapy before the platinum therapy discussed in previous exploratory aim; see Figure 2 for more details) to progression on that line of therapy. As date of progression of previous line therapies are not collected in the eCRF, start date of the following therapy will be used as the nearest surrogate.

PFI for penultimate platinum will be categorised as follows:

- Patients with bevacizumab maintenance and PFI between >6 and ≤12 months
- Patients without bevacizumab maintenance and PFI between >6 and ≤12 months
- Patients with bevacizumab maintenance and PFI >12 months
- Patients without bevacizumab maintenance and PFI >12 months

3.4.5 CA-125 progression

A blood sample for CA-125 will be taken at screening, starting treatment (day 1) and every 4 weeks until discontinuation of olaparib. When CA-125 assessment is performed, patients should be evaluated based on progressive serial elevation of serum CA-125 according to the Gynaecologic Cancer Inter Group (GCIG) criteria at the discretion of the investigator and according to local clinical practice.

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 criteria (Gordon et al 2011):

> A. Patients with elevated CA-125 pre-treatment (greater than the upper limit of normal (ULN) range) and normalization of CA-125 whilst on treatment (within normal range) must show evidence of CA-125 greater than, or equal to, 2 times the ULN range on 2 occasions at least 1 week apart or
>
> B. Patients with elevated CA-125 before treatment (greater than the ULN range), which never normalizes whilst on treatment (never within normal range), must show evidence of CA-125 greater than, or equal to, 2 times the pre-treatment nadir value on 2 occasions at least 1 week apart or
>
> C. Patients with CA-125 in the reference normal range before treatment must show evidence of CA- 125 greater than, or equal to, 2 times the ULN range on 2 occasions at least 1 week apart.

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

3.5 Safety endpoints

Safety and tolerability will be assessed in terms of adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESI), other significant adverse events (OAEs), laboratory data, and vital signs. These will be collected for all patients. In addition, safety analysis will also present treatment exposure, dose intensity and dose interruption.

3.5.1 Adverse Events

AEs and SAEs will be collected from time of signature of informed consent, throughout the treatment period and including the follow-up period (30 days after discontinuing olaparib except for AESIs). Investigators will report after the 30 day follow-up period if the patient has developed an AESI of Myelodysplastic syndrome (MDS) or Acute myeloid leukaemia (AML) or a new primary malignancy as well as pneumonitis.

Note, in screening part 1, only SAEs related to study procedures will be collected, see section 4 of the Clinical Study Protocol for more details. For AEs and SAEs definition, see section 6.1 to 6.2 of the Clinical Study Protocol.

3.5.2 Adverse Events of Special Interest (AESI)

AESI for olaparib are the important potential risks of MDS/AML, new primary malignancies (other than MDS/AML) and pneumonitis. AESI will be defined on the basis of AstraZeneca standard list of AE preferred terms for Olaparib studies.

A summary table will be produced capturing these toxicities of interest from first dose of olaparib until the end of the study (i.e. not restricted to treatment emergent AEs).
For more details of AESI, see section 6.3 of the Clinical Study Protocol.

3.5.3 Other Significant Adverse Events (OAEs)

For OAEs definition, see section 8.3.6 of the Clinical Study Protocol.

3.5.4 Laboratory safety assessments

Blood samples for determination of clinical chemistry and haematology will be taken within 7 days before starting olaparib and every 4 weeks until the safety follow-up 30 days after last dose of olaparib.

The following laboratory variables listed in Table 6 will be measured.

Table 6 Laboratory Safety Variables

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

3.5.5 Vital sign safety assessments

Vital signs will be measured at screening part 2 (for more details, see section 4 of the Clinical Study Protocol) and as clinically indicated thereafter.

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

Any clinically significant changes in vital signs should be recorded as an AE.

The following vital signs will be measured:

- Weight
- Blood Pressure (BP)
- Pulse

3.5.6 Calculation or derivation of safety variables

3.5.6.1 Exposure

The total treatment duration will be derived by using the following formula:

Total treatment duration (months) = (last dose date - first dose date +1) / (365.25/12)

The actual treatment duration is equal to the total treatment duration, excluding dose interruptions.

3.5.6.2 Compliance

The compliance with the therapy will be derived by using the following formula:

Therapy compliance (%) = 100 * (total dose received / total dose planned)

where

Total dose received = (number of days on treatment excluding interruptions * dose received per day)

Total dose planned = (number of days on treatment including interruptions * dose prescribed per day)

Days on treatment = date of last dose – date of first dose + 1

3.5.6.3 Dose intensity

Dose intensity will be derived by the following two standard definitions: relative dose intensity (RDI) and percentage intended dose (PID).

RDI is the percentage of the actual dose intensity delivered relative to the intended dose intensity through treatment discontinuation and will be derived by using the following formula:

RDI = 100% * d/D

where d is the actual cumulative dose delivered up to the earlier of progression (or a censoring event) or the actual last day of dosing and D is the intended cumulative dose up to the earlier of progression (or a censoring event) or the actual last day of dosing.

PID is the percentage of the actual dose delivered relative to the intended dose through progression and will be derived using the following formula:

PID = 100% * d/D

where d is the actual cumulative dose delivered up to progression (or a censoring event) and D is the intended cumulative dose up to progression (or a censoring event). D is the total dose that would be delivered, if there were no modification to dose or schedule.

Examples of dose intensity calculations can be found in appendix 5.

3.5.6.4 Dose interruption

Dose interruption will be captured on the eCRF as an action taken with the study drug.

3.5.6.5 AEs, SAEs, AESI and OAEs

All AEs, including SAEs, AESI and OAES, will be coded using MedDRA coding dictionary. The version of the MedDRA coding dictionary used will be specified in the data display footnote. All AEs will be tabulated by MedDRA System Organ Class (SOC) and Preferred Term (PT). SOC terms will be sorted alphabetically and then PT will be sorted in order of frequency of the total column within each SOC.

The grading scales found in the National Cancer Institute (NCI) CTCAE version 4.0 will be utilised for all AEs reported in the eCRF.

For each episode on an AE, all changes to the CTCAE version 4.0 grade attained as well as the maximum CTC grade should be reported.

In the summary tables, patients may be counted under multiple SOCs and PTs, but for each SOC and PT, patients are only counted once. If a patient experiences the same AE more than once (based on MedDRA PT), the maximum CTCAE grade for the event will be presented.

3.5.6.6 Laboratory assessments

Several blood samples for haematology and clinical chemistry could be collected within 7 days before starting olaparib. If a patient has more than one measurement, the latest measurement will be used in the summary table. All complete laboratory test results will be listed by patient and date.

3.5.6.7 Vital signs assessment

Height will be assessed at screening only. Weight will be assessed at screening and as clinically indicated at any other time. Body Mass Index (BMI) will be calculated at screening and as clinically indicated at any other time and presented as vital sign using the equation below:

BMI (kg/m^2) = Weight (Kg) / [Height (m) * Height (m)]

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

As vital signs (weight, BMI, BP and pulse) will be assessed as clinically indicated after screening (these are not assessed at scheduled visits), vital sign measurements will be listed only by patient and date.

4. ANALYSIS METHODS

All statistical computations and construction of tables, listings and figures will be performed using Statistical Analysis System (SAS) Version 9.4.

4.1 General Principles

Patient listings of key data represented in the electronic case report form (eCRF) will be provided. Measurements from patients excluded from the pre-defined analysis populations or extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables unless specified otherwise but will be included in the patient listings. This is not applicable for unscheduled tumour assessments that will be considered for PFS evaluation or for the additional reported PRO questionnaires (every 4 weeks) that will be presented int the tables. In general, the patient listings will be sorted by patient number and assessment date (and time), if applicable.

4.1.1 Rules for Reporting Statistics

Unless otherwise specified, continuous/quantitative variables will be summarized using descriptive statistics which will include the number of patients with data to be summarized (n), mean, standard deviation, median, minimum and maximum. The same number of decimal places as in the raw data will be presented when reporting minimum and maximum, one more decimal place than in the raw data will be presented when reporting mean and median, and two more decimal places than in the raw data will be presented when reporting standard deviation.

All categorical/qualitative data will be presented using frequency counts and percentage. Percentages equal to 100 will be presented as 100% and percentage will not be presented for 0 frequencies. Percentages will be rounded to 1 decimal place.

4.1.2 Rules for Handling Missing Data

Every effort will be made to capture all available data. Unless explicitly stated otherwise, missing data will not be imputed, and data will be presented and summarized as it is recorded in the database. However, if there is any date-related variable that is only partial, it will be imputed as follows to be used in the planned analysis.

The partial missing disease diagnosis dates will be imputed as per the following imputation rules.

Variable	Imputation of missing date
Disease diagnosis date	Month and year should be required in CRF. If day is missing, it will be imputed to 1st of month

The below partially missing dates of AEs and medications will be imputed as per the phUSE guidelines. Imputation rule is assuming the worst / make the most conservative judgment when imputing AEs and medications start/stop dates. Duration of AEs and medications will not be derived using imputed dates. The purpose of imputing a start date is to help define whether the AEs and medications started while taking the study drug

For missing start date:

- Missing day - Impute the 1st of the month unless month is same as month of first dose of study drug, then impute first dose date
- Missing day and month – impute 1st January unless year is the same as first dose date, then impute first dose date
- Completely missing – impute first dose date unless the end date suggests it could have started prior to this, in which case impute the 1st January of the same year as the end date.
- When imputing a start date ensure that the new imputed date is sensible i.e. is prior to the end date of the AE or medication.

For missing stop date:

- Missing day - Impute the last day of the month unless month is the same as month of last dose of study drug then impute last dose date. If last dose date occurs in a subsequent month then the last day of the month imputation will be kept.
- Missing day and month – impute 31st December unless year is the same as last dose date then impute last dose date
- Completely Missing – need to look at whether the AE/medication is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is marked or the ongoing flag is missing, then assume that AE is still present / medication is still being taken (i.e. do not impute a date). If the AE/medication has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after the first dose date, then impute the last dose date.

When dates and times are imputed, a flag should be provided to show that this is an imputed rather than actual date. The Clinical Data Interchange Standards Consortium Analysis Data Model has some rules to follow for both date and time imputations. Date imputation flags should have the name suffix –DTF and contain “D” for day, “M” for month, or “Y” for year.

Note that "M" implies that both the day and month are imputed, and "Y" implies day, month, and year are all imputed.

For some of the key date variables which require a full date in the CRF, those are not included in this section as no imputation is necessary. However, in some date-cases "unknown" could be provided for day; in that case, it will be imputed following the previous rules. For all other missing date-related variables, no imputation is envisioned since there is no planned analysis that requires an imputation.

4.1.3 Data cut-off

The data cut-off for the primary analysis of the study will occur after approximately 60% maturity of PFS in the s*BRCA* and all *BRCA* patient populations.

A final analysis of OS will occur after approximately 60% maturity of OS in the s*BRCA* and all *BRCA* patient populations.

4.1.4 Visit windows

Due to the practicality of scheduling patient visits, not all patients will have visits on the same study day. To allow for any presentations that summarize values by visit, visit windows will be defined according to Table 7. The upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2). The half way point is assumed to be the midpoint of the number of days between the visits, excluding both visit days (for example there are assumed to be 56 days between Day 56 and Day 112). If an odd number of days exist between two consecutive visits, then the upper limit is taken as the midpoint value plus 0.5 day.

Table 7 Visit Windows

Visit	Day	Laboratory/PRO assessments
Screening	Up to Day 1	(-28 : -1)
Day 1, Baseline	Day 1	(1 : 1)
Week 4	Day 29	(2 : 43)
Week 8	Day 57	(44 : 70)
Week 12	Day 85	(71 : 98)
Week 16	Day 113	(99 : 126)
Week 20	Day 141	(127: 154)
Week 24	Day 169	(155 : 182)
Week 28	Day 197	(183 : 210)
Week 32	Day 225	(211 : 238)
Week 36	Day 253	(239 : 266)
Week 40	Day 281	(267 : 294)
Week 44	Day 309	(295 : 322)
Week 48	Day 337	(323 : 350)
Week 52	Day 365	(351 : 378)
Week 56	Day 393	(379 : 406)
Week 60	Day 421	(407 : 434)
Week 64	Day 449	(435 : 462)
Week 68	Day 477	(463 : 490)
Week 72	Day 505	(491 :518)
Week 76	Day 533	(519 : 546)
Week 80	Day 561	(547 : 574)
Week 84	Day 589	(574 : 602)
Week 88	Day 617	(603 : 630)
Week 92	Day 645	(631 : 658)
Week 96	Day 673	(659 : 686)
Week 100	Day 701	(689 : 714)
Week 104	Day 729	(715 : 742)
Etc.		

Visit window (min : max)

Analysis visits will be applied to laboratory and PRO questionnaires assessments and determined based upon assessments dates and not on nominal visits designated in the database.

Note that PRO questionnaires were expected to be collected at baseline, at Day 29, then every 12 weeks (+/- 7 days) for 24 months or the data cut off for the final analysis, whichever comes first. However, as investigators reported PRO questionnaires more frequently, every 4 weeks, and that extra data will be presented in the tables, visit windows are calculated every 4 weeks for PRO questionnaires,

4.2 Descriptive Analysis

All descriptive analyses except 'patient disposition', which will be based on screened patients, will be based on the FAS. All descriptive analyses will be performed on *BRCA*m, s*BRCA*m, g*BRCA*m and HRRm^ patients (separately).

4.2.1 Patient Disposition

The following frequencies (number and percent) will be displayed in the *BRCA*m, s*BRCA*m, and g*BRCA*m patient disposition table by clinical study protocol version (patients screened before vs patients screened on or after protocol V2.0 22Dec2015), and HRRm^ patients:

- Patients screened
  - Patients included in the FAS
  - Patients excluded from the FAS (and reasons)
  - Patients included in the safety analysis set
  - Patients excluded from the safety analysis set (and reasons)

The denominators for the percent calculations will be the number of patients screened, whether or not they are included in any of the analyses.

A summary of the number of patients who discontinued treatment and who terminated the study will be presented. The following frequencies (number and percent) will be displayed in the patient disposition table:

- Patients included in the FAS
  - Patients ongoing in the study
  - Patients terminated from the study (and reasons)
  - Patients ongoing study treatment
  - Patients who discontinued the treatment (and reasons)

The denominators for the percent calculations will be the number of patients enrolled in the study and are in the FAS.

Additionally, follow-up time will also be summarized. The follow-up time will be calculated as the median time from the date of enrolment to death or censoring in all patients. 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.

A listing of disposition will be provided for all patients.

4.2.2 Protocol deviations

A listing of important protocol deviations will be provided for all patients in the FAS with important protocol deviations. The number of patients with at least one important protocol deviation and the corresponding count and percentage of patients in each important protocol deviation category will be summarized.

4.2.3 Demographics and Baseline Characteristics

Baseline is defined to be the last evaluable visit prior to starting treatment.

Demographics and baseline characteristics will be listed and summarized for all patients in the FAS. Demographic characteristics will include age, sex, race, ethnicity, height, and weight. Age will be calculated using the equation below:

Age = (date of informed consent – date of birth + 1) / 365.25 and truncated to complete years.

Baseline characteristics will include:

- General pathology characteristics
- Family history of cancer
- Breast cancer gene status
- Eastern Cooperative Oncology Group (ECOG) performance status

4.2.4 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The version of the coding dictionary used will be included in a footnote on the output. Coded medical history terms will be summarized for the full analysis set, by MedDRA System Organ Class (SOC) and Preferred Term (PT). SOC terms will be sorted alphabetically and then preferred term will be sorted in order of frequency of the total column within each SOC.

Patient listings of coded medical history terms will be provided.

4.2.5 Medication

A summary of the prior and concomitant medication received will be provided. Medications (prior, concomitant) will be coded using the World Health Organization Drug Dictionary (WHODrug). The WHODrug version used will be specified in the data display footnote. Prior and concomitant medications will be listed separately and sorted alphabetically by Anatomical Therapeutic Chemical (ATC) class (and preferred drug name).

Prior medications are defined as medications taken prior to date of first dose of olaparib (date of last medication dose or end medication before date of first dose of treatment) and

concomitant medications are defined as medications that are taken on or after date of first dose of olaparib.

4.3 Primary Analysis: PFS

The primary analysis will be performed when approximately 60% maturity of PFS has been observed in s*BRCA*m patients, and when approximately 60% maturity of PFS has been observed in all *BRCA*m patients. For details about PFS definition based on investigator assessment according to RECIST 1.1 see section 3.2.1.

4.3.1 Real-world clinical effectiveness of olaparib by investigator assessed PFS in patients with *BRCA*m ovarian cancer using RECIST criteria

This primary analysis will be performed on *BRCA*m patients based on the FAS using investigator assessment of PFS according to RECIST 1.1guidelines.

PFS will be summarized using the total number and percentage of subjects experiencing a PFS event, the type of event (RECIST progression or death in absence of progression), the number and percentage of censored patients, the number and percentage of progression-free subjects at time of the analysis, patients who are lost to follow-up and patients who withdrew consent.

In addition, the PFS rate and associated 95% CI will be summarized at six-monthly intervals using the Kaplan-Meier (KM) method. The median PFS and corresponding 95% CI (whenever estimable) and the median follow-up time in censored patients (in months) will also be presented. A KM plot of PFS will be presented.

4.3.2 Subgroups analysis of PFS in patients with *BRCA*m ovarian cancer using RECIST criteria

Subgroup analyses are considered exploratory analyses. These will be performed on *BRCA*m patients based on the FAS.

Subgroup analysis will be performed for the PFS endpoint to assess the consistency of olaparib effect across important clinical characteristics. The following subgroups will be summarised:

- g*BRCA*m
- Response to previous platinum chemotherapy (CR vs PR).
- Time to disease progression on penultimate platinum chemotherapy (6 – 12 months vs > 12 months) (as disease progression on penultimate platinum chemotherapy is not reported in the eCRF, time to disease progression will be approximated using time from first dose of penultimate platinum chemotherapy to first dose of last platinum chemotherapy).
- Measurable disease, non-measurable disease, and NED at baseline.

- *BRCA* mutation type: g*BRCA: BRCA*1, *BRCA*2, *BRCA*1-2 (both).
- Age at enrolment (<65 vs. ≥65 years old).
- Region (Eastern Europe vs Western Europe/Canada). Western Europe includes: Italy, Spain, UK. Eastern Europe includes: Bulgaria, Czech Republic, Hungary, Poland.
- Family history of ovarian/breast cancer (Yes/No).
- Prior bevacizumab use (Yes/No).
- Number of prior chemotherapy lines (≤3, ≥4).

For each subgroup analysis KM curves and median PFS and 95%CI will be presented.

4.3.3 Sensitivity analysis of PFS in patients with *BRCA*m ovarian cancer

Sensitivity analyses are considered exploratory analyses. These will be performed on *BRCA*m patients based on the FAS.

- Sensitivity analysis for PFS in patients with *BRCA*m ovarian cancer will be performed to assess attrition bias. Patients who take subsequent anti-cancer therapy prior to progression or death will be censored at the last available tumour assessment date prior to the date of subsequent anti-cancer therapy and those who miss > 1 assessment visit will not be censored.
- Additionally, a descriptive analysis of demographic and baseline characteristics for patients prematurely censored and not prematurely censored for PFS in patients with *BRCA*m ovarian cancer will be performed. A patient is defined as prematurely censored if they had not progressed (or died in the absence of progression) and the latest scan prior to date cut-off (DCO) was more than one scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date.

4.3.4 Real-world clinical effectiveness of olaparib by investigator assessed PFS in patients with s*BRCA*m using RECIST criteria

This primary analysis will be performed on s*BRCA*m patients based on the FAS using investigator assessment of PFS according to RECIST 1.1 guidelines.

PFS will be summarized in the same way as described in section 4.3.1. A KM curve of PFS for the s*BRCA*m group of patients will be presented.

4.4 Secondary Analysis

4.4.1 Real-world clinical effectiveness of olaparib by assessment of OS

OS will be analysed in *BRCA*m and s*BRCA*m as well as g*BRCA*m patients separately based on the FAS. OS will be summarized in the same way as PFS as described in section 4.3.1 with the exception that the only event considered is death. KM plots will be presented. In addition, the median follow-up time in censored (in months) will also be presented.

4.4.2 Real-world clinical effectiveness of olaparib by assessment of PFS2

PFS2 will be analysed in *BRCA*m and s*BRCA*m as well as g*BRCA*m patients separately based on the FAS. PFS2 will be summarized in the same way as PFS as described in section 4.3.1 with the exception that the number and % of patients with 'second progression' will replace RECIST progression events in the table. KM plots will also be presented.

4.4.3 Real-world clinical effectiveness of olaparib by assessment of TFST

TFST will be analysed in *BRCA*m and s*BRCA*m as well as g*BRCA*m patients separately based on the FAS. TFST will be summarized in the same way as PFS as described in section 4.3.1 with the exception that the number and % of patients 'commencing subsequent anti-cancer therapy' will replace RECIST progression events in the table. KM plots will also be presented.

4.4.4 Real-world clinical effectiveness of olaparib by assessment of TSST

TSST will be analysed in *BRCA*m and s*BRCA*m as well as g*BRCA*m patients separately based on the FAS. TSST will be summarized in the same way as PFS as described in section 4.3.1 with the exception that the number and % of patients 'commencing second subsequent anti-cancer therapy' will replace RECIST progression events in the table. KM plots will also be presented.

4.4.5 Real-world clinical effectiveness of olaparib by assessment of TDT

TDT will be analysed in *BRCA*m and s*BRCA*m as well as g*BRCA*m patients separately based on the FAS. TDT will be summarized in the same way as PFS as described in section 4.3.1 with the exception that the number and % of patients 'discontinuing olaparib' will replace RECIST progression events in the table. KM plots will also be presented.

4.4.6 Nature and patterns of AEs of nausea and vomiting and their impact on QoL and toxicity management patterns used in routine clinical practice

The safety and tolerability analysis of olaparib maintenance therapy, including AEs of nausea and vomiting, are assessed and presented in section 4.6 (Safety analysis).

The impact of nausea and vomiting on Qol, using FLIE questionnaire, is assessed and presented in section 4.4.7.1 (Functional living index emesis).

A summary of concomitant medication received will be provided, see section 4.2.5 for further details.

4.4.7 QoL of patients

4.4.7.1 Functional Living Index Emesis (FLIE)

This exploratory analysis will be performed on *BRCA*m and s*BRCA*m as well as g*BRCA*m patients separately based on the FAS.

The total score of the FLIE questionnaire and change from baseline will be summarized using descriptive statistics and presented for each follow-up time point. Furthermore, overall compliance and compliance over time will be also summarized using frequency counts and percentages (for definition of compliance of PRO please see section 3.3.6.1).

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

This exploratory analysis will be performed on *BRCA*m and s*BRCA*m as well as g*BRCA*m patients separately based on the FAS.

To assess and describe the patient-reported health-related quality of life (HRQoL) the Trial Outcome Index (TOI) score and change from baseline will be summarized using descriptive statistics and presented for each follow-up time point including data post progression where available (up to 24 months collection).

Visit response based on change from baseline of TOI score (improved, worsened, no change) will be summarized using frequency counts and percentages for each follow-up time point (for further information about visit response definitions please see section 3.3.6.3).

Best overall TOI score response (improved, worsened, no change, other) will be summarized using frequency counts and percentages (for further information about best overall TOI response definitions please see section 3.3.6.3).

FACT-O total score and changes from baseline will also be summarized using descriptive statistics and presented for each follow-up time point.

Furthermore, overall compliance and compliance over time will be also summarized using frequency counts and percentages (for definition of compliance of PRO please see section 3.3.6.1).

4.4.7.3 Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

This exploratory analysis will be performed on *BRCA*m and s*BRCA*m as well as g*BRCA*m patients separately based on the FAS.

FACIT-F total score and changes from baseline will also be summarized using descriptive statistics and presented for each follow-up time point (for further information about FACIT-F total score definition please see section 3.3.6.4). Furthermore, overall compliance and compliance over time will be also summarized using frequency counts and percentages (for definition of compliance of PRO please see section 3.3.6.1).

4.4.7.4 ORZORA QoL Additional Items Questionnaire

This exploratory analysis will be performed on *BRCA*m and s*BRCA*m as well as g*BRCA*m patients separately based on the FAS.

The answers of the first 7 additional ovarian cancer items will be summarized using frequency and percentage at baseline and for each follow-up time point. The answers of the last free text item will be listed (for further information about the newly developed ovarian cancer items please see section 3.3.6.5). Furthermore, overall compliance and compliance over time will be also summarized using frequency counts and percentages (for definition of compliance of PRO please see section 3.3.6.1).

Table 8 below provides a summary of the efficacy and Qol analyses.

Table 8 Table of efficacy and Qol analyses and pre-planned sensitivity, subgroup analyses

Study objectives	Analyses Notes
Primary objectives	
To assess the real-world clinical effectiveness of olaparib maintenance monotherapy by investigator assessed progression free survival (PFS) according to RECIST 1.1 in patients with *BRCA*m ovarian cancer	Primary Analysis Endpoint: PFS PFS Assessment: Investigator-assessed PFS according to RECIST 1.1 Population: Full Analysis Set Patient Group: *BRCA*m Analysis Method: KM plot , median PFS and 95%CI will be provided as well as the PFS rate and 95% CI at six-monthly intervals using KM method. Subgroups analyses and sensitivity analyses below are considered supportive Subgroup Analyses: g*BRCA*m Response to previous platinum chemotherapy (CR vs PR). Time to PD on penultimate platinum chemotherapy (6 – 12 months / > 12 months) (as disease progression on penultimate platinum chemotherapy is not reported in the eCRF, time to disease progression will be approximated using time from first dose of penultimate platinum chemotherapy to first dose of last platinum chemotherapy). Measurable disease, non-measurable disease, and NED at baseline. *BRCA* mutation type: g*BRCA* (based on RECIST), *BRCA*1, *BRCA*2, *BRCA*1-2 (both). Age at enrolment (<65 vs. ≥65 years old). Region (Eastern Europe vs Western Europe/Canada). Family history of ovarian/breast cancer (Yes/No). Prior bevacizumab use (Yes/No). Number of prior chemotherapy lines (≤3, ≥4). Median PFS and 95%CI, PFS rate and 95%CI at six-monthly intervals

Study objectives	Analyses Notes
	and KM plot will be provided Sensitivity Analyses: PFS recalculation to assess attrition bias: *BRCA*m patients who take subsequent anti-cancer therapy prior to progression will be censored and those who miss > 1 assessment visit will not be censored. • KM plot, median PFS and 95%CI will be provided. PFS analysis of patients prematurely censored: *BRCA*m patients who have not progressed (or died in the absence of progression) and the latest scan prior to DCO was more than one scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date. • Descriptive summary only
To assess the real-world clinical effectiveness of olaparib maintenance monotherapy by investigator assessed progression free survival (PFS) according to modified Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 in patients with s*BRCA*m ovarian cancer	Endpoint: PFS PFS Assessment: Investigator-assessed PFS according to RECIST 1.1 Population: Full Analysis Set Patient Group: s*BRCA*m Analysis Method: Median PFS and 95%CI, PFS rate and 95%CI at six-monthly intervals, and KM plot will be provided
Secondary objectives	
To assess the real-world clinical effectiveness of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer, by assessment of: a) overall survival (OS), b) time to investigator-assessed second progression (PFS2), or death, in patients with *BRCA*m ovarian cancer.	Endpoints: OS and PFS2 Population: Full Analysis Set Patient Group: *BRCA*m, g*BRCA*m and s*BRCA*m (separately) Analysis Method: Median PFS2/OS and 95%CI, OS/PFS2 rate and 95%CI at six-monthly intervals, and KM plot will be provided
To assess the real-world clinical effectiveness of olaparib maintenance monotherapy in patients	Endpoints: TFST, TSST and TDT Population: Full Analysis Set

Study objectives	Analyses Notes
with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer, by assessment of a) time to first subsequent therapy or death (TFST), b) time to second subsequent therapy or death (TSST) and c) time to olaparib discontinuation or death (TDT) in patients with *BRCA*m ovarian cancer	Patient Group: *BRCA*m, g*BRCA*m and s*BRCA*m (separately) Analysis Method: Median TFST/TSST/TDT and 95%CI, TFST/TSST/TDT rate and 95%CI at six-monthly intervals, and KM plot will be provided
To assess and describe the quality of life (QoL) of patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer.	Endpoints: FLIE, FACT-O, FACIT-F, ORZORA Qol (additional ovarian cancer items) Population: Full Analysis Set Patient Group: *BRCA*m, g*BRCA*m and s*BRCA*m (separately) Analysis Method of FLIE and FACIT-F: Total score and change from baseline will be summarize using descriptive statistics and presented for each follow-up time point Analysis Method of FACT-O: TOI score and change from baseline will be summarize using descriptive statistics and presented for each follow-up time point Visit response based on change from baseline of TOI score (improved, worsened, no change) will be summarized using frequency counts and percentages for each follow-up time point Best overall TOI score response (improved, worsened, no change, other) will be summarized using frequency counts and percentages FACT-O total score and change from baseline will be summarize using descriptive statistics and presented for each follow-up time point Analysis Method of ORZORA Qol: Additional ovarian cancer items will be summarized using frequency and percentage at baseline and for each follow-up time point

4.5 Exploratory Analysis

4.5.1 The long-term safety of olaparib, including follow up for MDS/AML, New primary malignancies and pneumonitis

This exploratory analysis will be performed on all patients based on the safety analysis set. Patients with *BRCA*1 alone, *BRCA*2 alone or both mutations will be identified.

For pharmacovigilance purpose and characterisation of events of special interest, the number and proportions of patients who developed MDS/AML, new primary malignancies and pneumonitis will be summarized.

In the summary tables, frequencies and percentages of patients for each event separately (MDS/AML, new primary malignancies, and pneumonitis) will be presented in the form of absolute percentage and in terms of 100 patient years. Note that patients with multiple events (MDS/AML, new primary malignancies and pneumonitis) will be only counted once within each subtype and percentages will be calculated for all patients in the safety analysis set.

Incidence rates of each event separately (MDS/AML, new primary malignancies, and pneumonitis) per 100 patient years will also be presented, respectively. Incidence rate is calculated as follows:

Incidence rates = 100 * (number of events / total patient years at risk)

Total patient years at risk is calculated as a sum of the follow-up period for each patient:

- For patients with the event in question: time from first dose to the event in question.
- For patients without the event in question: time from first dose to earliest of date last known to be alive or date of termination

Number of events is the count of each individual event (MDS/AML, new primary malignancies, and pneumonitis) including recurrent event per subject.

4.5.2 Incidence of side effects and QoL according to age and the presence of comorbidities

The incidence of side effects according to age and the presence of comorbidities (as collected in the medical history table in the CRF) are assessed and presented in section 4.6.5.

QoL according to age will be performed on *BRCA*m patients based on the FAS. The total score of FLIE, FACT-O (including TOI score) and FACIT-F questionnaires and changes from baseline will be summarized by age group (< 65 years, ≥ 65 years) using descriptive statistics and presented for each follow-up time point.

Standard summaries of AEs, QoL and medical history (see sections 4.6.5, 3.3.6 and 4.2.4) will facilitate a descriptive exploration of this exploratory endpoint.

4.5.3 Clinical effectiveness of (response to) subsequent line of treatment and correlating it with the PFI (artificial prolongation of PFI through olaparib)

This exploratory analysis will be performed on *BRCA*m patients based on the FAS. However, patients who have died before progression on olaparib, have not progressed at the time of analysis or have not received a subsequent line of therapy for any other reason will not be included in this exploratory analysis.

The best response to subsequent first line therapy post olaparib will be summarized using frequency and percentage of patients for each PFI with olaparib category and overall (see section 3.4.3 for PFI with olaparib category definitions).

4.5.4 Efficacy of olaparib according to the previous therapy, with or without bevacizumab, and according to the PFI (recurrence during or after the end of bevacizumab maintenance)

This exploratory analysis will be performed on *BRCA*m patients based on the FAS.

The penultimate PFI will be used in this analysis. For each penultimate PFI category with and without bevacizumab, the number of patients and number of PFS events will be summarized (see section 3.4.4 for penultimate PFI category definition). KM curves and median PFS and 95% CIs will be presented.

4.5.5 Activity of olaparib according to the germline mutational status (*BRCA*1 vs 2), and to the presence of family history of ovarian/breast cancer (yes vs no)

Consistency of Olaparib effect on PFS across germline mutational status (*BRCA*1 vs 2) and the presence of family history (yes/no) will be assessed. Subgroup analysis of PFS are presented for patients who had g*BRCA*, *BRCA*1, *BRCA*2 and *BRCA*1-2 (both) mutational status and by presence or non-presence of family history of ovarian/breast cancer in section 4.3.2.

4.5.6 Kinetic of Ca125 progression according to GCIG criteria and its correlation with disease progression by RECIST during olaparib therapy

This exploratory analysis will be performed on *BRCA*m patients based on the FAS.

The number and percentage of patients who progressed and did not progress according to CA-125 (as defined in section 3.4.5) versus progression or non-progression via RECIST during olaparib therapy will be summarized using a 2x2 contingency table.

4.5.7 Real-world clinical effectiveness of olaparib by assessment of PFS in patients with HRRm^ ovarian cancer

This exploratory analysis will be performed on HRRm^ patients based on the FAS using investigator assessment of PFS according to RECIST 1.1 guidelines.

PFS will be summarized in the same way as described in section 4.3.1. A KM plot of PFS will also be presented.

4.5.8 Real-world clinical effectiveness of olaparib by assessment of OS in patients with HRRm^ ovarian cancer

OS will be analysed in HRRm^ patients based on the FAS. OS will be summarized in the same way as PFS as described in section 4.3.1 with the exception that the only event considered is death. KM plots will also be presented.

4.6 Safety Analysis

All safety analyses will be based on the safety analysis set and will be performed on patients with *BRCA*m, s*BRCA*m, g*BRCA*m and HRRm^ ovarian cancer (separately).

4.6.1 Exposure

The duration of exposure will be summarized by presenting summary statistics of the total treatment duration and actual treatment duration (for more details of exposure definition please see section 3.5.6.1).

4.6.2 Compliance

Compliance will be summarized by presenting summary statistics of the percentage of therapy compliance (100*(total dose received / total dose planned)) (for more details of compliance definition please see section 3.5.6.2).

4.6.3 Dose intensity

Dose intensity will be summarized by presenting summary statistics of the RDI and PID (for more details of RDI and PDI definitions please see section 3.5.6.3).

4.6.4 Dose interruptions/Reductions

The total number of dose interruptions per patient will be summarized by presenting summary statistics (mean, standard deviation, median, minimum, maximum). Additionally, the number of patients with a dose interruption will be summarised using frequency and percentages for the following categories: none, 1, 2, and 3 or more dose interruptions.

In addition, the number of patients with a dose reduction will be summarized using frequency and percentages for the following categories: none, 1 dose reduction, and more than 1 dose reductions.

4.6.5 Adverse Events (AEs)

The term AE is used to include both serious and non-serious AEs (for more details of AE definition please see section 3.5).

All AEs will be tabulated by MedDRA SOC and PT. AEs occurring before treatment with olaparib will be included in the data listings but will not be included in the summary tables of AEs, except for AEs occurring before olaparib treatment with AE which worsen (by investigator report of a change in intensity) at or after start of the first dose of olaparib. Any AE occurring within 30 days of discontinuation of olaparib will be included in the AE

summaries. Any AE occurring 30 days after discontinuation of olaparib will be included in the data listings but will not be included in the summary tables of AEs.

All AEs and separately all AEs with outcome of death, all SAEs, all AEs leading to olaparib discontinuation will be tabulated by MedDRA SOC and PT. SOC terms will be sorted alphabetically and then PT will be sorted in order of frequency of the total column within each SOC. In the summary tables, patients may be counted under multiple SOCs and PTs, but for each SOC and PT, patients are only counted once. If a patient experiences the same AE more than once (based on MedDRA PT), the maximum CTCAE grade for the event will be presented.

The following summary tables will be generated using number and percentage of patients and number of events:

- All AEs
- All AEs with causality related to olaparib*
- All SAEs
- All SAEs with causality related to olaparib*
- All OAEs
- All AEs leading to olaparib interruption
- All AEs leading to olaparib interruption and with causality related to olaparib*
- All AEs with an outcome of death
- All AEs with an outcome of death and with causality related to olaparib*
- All AEs with CTCAE grade 3 or higher
- All AEs with CTCAE grade 3 or higher and with causality related to olaparib*
- All AEs leading to olaparib discontinuation
- All AEs with the maximum reported CTCAE grade
- All AEs according to age group (< 65 years, ≥ 65 years)
- All AEs according to the presence of comorbidities (presence/absence of additional disorders)

* as assessed by the investigator.

Summary tables will also be produced for the following common olaparib AEs, based on grouped preferred terms:

- Anaemia
- Neutropenia

- Thrombocytopenia
- Nausea
- Vomiting
- Fatigue/Asthenia

The AEs will be listed by patient including: verbatim term, SOC, PT, AE start-stop dates, max CTCAE grade, SAE (Y/N), causality olaparib (Y/N), action taken with regard to olaparib, AE caused patient´s withdrawal from study (Y/N), outcome.

4.6.6 Adverse Events Special Interest (AESIs)

The term AESI is used to include the important potential risks of MDS/AML, new primary malignancies (other than MDS/AML) and pneumonitis (for more details of AESI definition please see section 3.5.2).

All AESIs will be tabulated by MedDRA SOC and PT. AESIs occurring before treatment with olaparib will be included in the data listings but will not be included in the summary tables of AESIs, except for AESIs occurring before olaparib treatment with AESI which worsen (by investigator report of a change in intensity) at or after start of the first dose of olaparib.

A summary table will be produced capturing these toxicities.

4.6.7 Laboratory Results

Blood samples for haematology and clinical chemistry will be collected within 7 days before starting olaparib (if a patient shows more than one measurement, the latest measurement will be used), and every 4 weeks until the safety follow-up 30 days after last dose of olaparib.

All laboratory results and change from baseline in haematology and clinical chemistry will be summarized using descriptive statistics (n, mean, standard deviation, median, lower and upper quartile) and presented by visit.

A table will be produced showing the number of patients with maximum on-treatment ALT and AST values greater than 3, 5 and 10 times the upper limit of the local laboratory reference ranges. This summary will be produced overall and also split by maximum total bilirubin (TBL) values greater than 2 times the upper limit of the local laboratory reference range.

Plots of ALT vs TBL will also be produced with reference lines at 3×ULN for ALT, and 2×ULN for TBL. Plots of AST vs TBL will also be produced with reference lines at 3×ULN for AST, and 2×ULN for TBL, where necessary. In each plot, TBL will be in the vertical axis.

A shift table will be produced showing the number and percentage of patients switching from normal, abnormal and not done laboratory results at baseline (the last lab result obtained prior to the start of olaparib treatment) to the maximum value on treatment (classified as normal, abnormal and not done).

A shift table for haemoglobin, leukocytes, neutrophils, and platelets will be produced showing the number and percentage of patients switching from normal, abnormal and not done laboratory results at baseline (the last lab result obtained prior to the start of olaparib treatment) to the minimum value on treatment (classified as normal, abnormal and not done).

The complete laboratory test results will be listed by patient and date.

4.6.8 Vital Signs

Vital signs parameter values (weight, BMI, BP, and pulse) will be obtained at the screening visit and clinically indicated thereafter (the date of collection and measurement will be recorded on the appropriate eCRF). As vital signs data are not collected at scheduled time points, vital sign measurements will be listed only by patient and date.

5. INTERIM ANALYSES

No interim analysis is planned for this study.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The following changes of analysis from protocol were applied.

Protocol	Analysis
Protocol section 4: QoL questionnaires will be collected at baseline, at Day 29, then every 12 weeks (+/- 7 days) for 24 months or the data cut off for the final analysis, whichever comes first.	SAP section 4.1.4: Visit windows for QoL questionnaires were derived at baseline, at day 29, then every 4 weeks for 24 months or data cut off for the final analysis, whichever come last. Reason: Investigators reported more frequently Qol questionnaires than expected initially in the protocol. As the data was collected, it was decided to report all the visits outputs.
Protocol section 8.4.3 Subgroup analysis: Time to disease progression on last platinum based chemotherapy received prior to first dose of olaparib (6-12 months / >12 months)	SAP section 4.3.2: Time to disease progression on penultimate platinum chemotherapy (6-12 months / > 12 months). Reason: Clarification of the time period intended as the language was not clear

7. REFERENCES

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http://www.phusewiki.org/wiki/index.php?title=Imputing_Partial_Dates

8. APPENDIX

Appendix 1: FLIE questionnaire from the eCRF

FLIE-Functional Living Index Emesis

Date of completion	__ / __ / ____
1 How much nausea have you had in past 3 days?	○ None ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ A great deal
2 Has nausea affected your ability to maintain usual recreation or leisure activities in the past 3 days?	○ Not at all ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ A great deal
3 Has nausea affected your ability to make a meal or do minor household repairs during the past 3 days?	○ A great deal ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ Not at all
4 How much has nausea affected your ability to enjoy a meal in the past 3 days?	○ Not at all ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ A great deal
5 How much has nausea affected your ability to enjoy liquid refreshment in the past 3 days?	○ Not at all ○ 2

	○ 3 ○ 4 ○ 5 ○ 6 ○ A great deal
6 How much has nausea affected your willingness to see and spend time with family and friends, in the past 3 days?	○ A great deal ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ Not at all
7 Has nausea affected your daily functioning in the past 3 days?	○ Not at all ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ A great deal
8 Rate the degree to which your nausea has imposed a hardship on you (personally) in the past 3 days.	○ Not at all ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ A great deal
9 Rate the degree to which your nausea has imposed a hardship on those closest to you in the past 3 days	○ Not at all ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ A great deal
10 How much vomiting have you had in the past 3 days?	○ None ○ 2 ○ 3 ○ 4 ○ 5 ○ 6

	○ A great deal
11 Has vomiting affected your ability to maintain usual recreation or leisure activities during the past 3 days?	○ A great deal ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ Not at all
12 Has vomiting affected your ability to complete your usual household tasks during the past 3 days?	○ Not at all ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ A great deal
13 How much has vomiting affected your ability to enjoy a meal in the past 3 days?	○ Not at all ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ A great deal
14 How much has vomiting affected your ability to enjoy liquid refreshment in the past 3 days?	○ Not at all ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ A great deal
15 How much has vomiting affected your willingness to see and spend time with friends, in the past 3 days?	○ A great deal ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ Not at all
16 Has vomiting affected your daily functioning during the past 3 days?	○ Not at all ○ 2 ○ 3

	○ 4 ○ 5 ○ 6 ○ A great deal
17 Rate the degree to which your vomiting has imposed a hardship on you (personally) in the past 3 days.	○ Not at all ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ A great deal
18 Rate the degree to which your vomiting has imposed a hardship on those closest to you in the past 3 days.	○ A great deal ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ Not at all

Appendix 2: FACT-O questionnaire from the eCRF and scoring guidelines

Functional Assessment of Cancer Therapy-Ovarian (symptoms in past 7 days)

Date of completion	__ / __ / ____
Physical well-being (PWB)	
1 I have a lack of energy (GP1)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
2 I have nausea (GP2)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
3 Because of my physical condition, I have trouble meeting the needs of my family (GP3)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
4 I have pain (GP4)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
5 I am bothered by side effects of treatment (GP5)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
6 I feel ill (GP6)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much

7 I am forced to spend time in bed (GP7)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
Social/Family well-being (SWB)	
8 I feel close to my friends (GS1)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
9 I get emotional support from my family (GS2)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
10 I get support from my friends (GS3)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
11 My family has accepted my illness (GS4)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
12 I am satisfied with family communication about my illness (GS5)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
13 I feel close to my partner (or the person who is my main support) (GS6)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
14 Declined satisfied with sex life (GS7)	○ Declined to Answer
14 I am satisfied with my sex life (GS7)	○ Not At All

	○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
Emotional well-being (EWB)	
15 I feel sad (GE1)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
16 I am satisfied with how I am coping with my illness (GE2)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
17 I am losing hope in the fight against my illness (GE3)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
18 I feel nervous (GE4)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
19 I worry about dying (GE5)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
20 I worry that my condition will get worse (GE6)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
Functional well-being (FWB)	
21 I am able to work (include work at home) (GF1)	○ Not At All ○ A Little Bit

	○ Somewhat ○ Quite A Bit ○ Very Much
22 My work (include work at home) is fulfilling (GF2)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
23 I am able to enjoy life (GF3)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
24 I have accepted my illness (GF4)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
25 I am sleeping well (GF5)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
26 I am enjoying the things I usually do for fun (GF6)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
27 I am content with the quality of my life right now (GF7)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
Additional concerns (OCS)	
28 I have swelling in my stomach area (O1)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit

	○ Very Much
29 I am losing weight (C2)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
30 I have control of bowels (C3)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
31 I have been vomiting (O2)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
32 I am bothered by hair loss (B5)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
33 I have a good appetite (C6)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
34 I like the appearance of my body (C7)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
35 I am able to get around by myself (BMT5)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
36 I am able to feel like a woman (B9)	○ Not At All ○ A Little Bit

	○ Somewhat ○ Quite A Bit ○ Very Much
37 I have cramps in my stomach area (O3)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
38 I am interested in sex (BL4)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
39 I have concerns about my ability to have children (BMT7)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much

FACT-O Scoring Guidelines (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-O).
5. The higher the score, the better the QOL**.**

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL WELL-BEING (PWB) Score range: 0-28	GP1	4	-	_____	=_____
	GP2	4	-	_____	=_____
	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____
				Sum individual item scores: _____	
				Multiply by 7: _____	
	Divide by number of items answered: _____= **PWB subscale score**				
SOCIAL/FAMILY WELL-BEING (SWB) Score range: 0-28	GS1	0	+	_____	=_____
	GS2	0	+	_____	=_____
	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____
				Sum individual item scores: _____	
				Multiply by 7: _____	
	Divide by number of items answered: _____= **SWB subscale score**				
EMOTIONAL WELL-BEING (EWB) Score range: 0-24	GE1	4	-	_____	=_____
	GE2	0	+	_____	=_____
	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____
				Sum individual item scores: _____	
				Multiply by 6: _____	
	Divide by number of items answered: _____= **EWB subscale score**				

FUNCTIONAL WELL-BEING (FWB) Score range: 0-28	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____ = **FWB subscale score**

FACT-O Scoring Guidelines (Version 4) – Page 2

Subscale	Item Code	Reverse item?		Item response	Item Score
OVARIAN CANCER SUBSCALE (OCS) Score range: 0-44	O1	4	-	_____	=_____
	C2	4	-	_____	=_____
	C3	0	+	_____	=_____
	O2	4	-	_____	=_____
	B5	4	-	_____	=_____
	C6	0	+	_____	=_____
	C7	0	+	_____	=_____
	BMT5	0	+	_____	=_____
	B9	0	+	_____	=_____
	O3	4	-	_____	=_____
	BL4	0	+	_____	=_____
	BMT7	NOT CURRENTLY SCORED			

Sum individual item scores: _____

Multiply by 11: _____

Divide by number of items answered: _____ = **OC subscale score**

To derive a FACT-O Trial Outcome Index (TOI):

Score range: 0-100

_____	+ _____	+ _____	= _____	=**FACT-O TOI**
(**PWB** score)	(**FWB** score)	(**OCS** score)		

To derive a FACT-G total score:

Score range: 0-108

_____ + _____ + _____ + _____ = _____ =**FACT-G Total**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To derive a FACT-O total score:

Score range: 0-152

_____ + _____ + _____ + _____ + _____ = _____ =**FACT-O Total**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**OCS** score)

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

Appendix 3: FACIT-Fatigue questionnaire from the eCRF and scoring guidelines

Functional Assessment of Chronic Illness Therapy-Fatigue (symptoms in past 7 days)

Date of completion	__ / __ / ____
1 I feel fatigued (HI7)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
2 I feel weak all over (HI12)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
3 I feel listless (“washed out”) (AN1)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
4 I feel tired (AN2)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
5 I have trouble starting things because I am tired (AN3)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
6 I have trouble finishing things because I am tired (AN4)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much

7 I have energy (AN5)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
8 I am able to do my usual activities (AN7)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
9 I need to sleep during the day (AN8)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
10 I am too tired to eat (AN12)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
11 I need help doing my usual activities (AN14)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
12 I am frustrated by being too tired to do the things I want (AN15)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
13 I have to limit my social activity because I am tired (AN16)	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much

FACIT-Fatigue Scale (version 4) Scoring Guidelines

Items are scored as follows: 4=Not At All; 3=A Little Bit; 2=Somewhat; 1=Quite A Bit; 0=Very Much, EXCEPT items #7 and #8 which are reversed scored. Score range 0-52.

A score of less than 30 indicates severe fatigue. The higher the score, the better the quality of life.

Item Number	Reverse Item?		Item Response	Item Score
1	4	-		=
2	4	-		=
3	4	-		=
4	4	-		=
5	4	-		=
6	4	-		=
7	0	+		=
8	0	+		=
9	4	-		=
10	4	-		=
11	4	-		=
12	4	-		=
13	4			=

Sum individual item scores: _____

Multiply by 13: _____

Divide by number of items answered: _____

For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines on-line at www.facit.org.

Appendix 4: ORZORA Qol: Additional Ovarian Cancer Items from the eCRF

ORZORA QoL additional items questionnaire (symptoms in past 7 days)

Date of completion	__ / __ / ____
1 I feel ill with low energy	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
2 I am able to enjoy life and I am still interested in my hobbies and interests feel	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
3 I am satisfied that my family understands my disease	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
4 I feel I am able to meet the needs of my family	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
5 I understand the need to take my medication and my treatment regimen	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
6 My treatment has had significantly negative effects on my QoL	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much

7 I feel like a normal woman	○ Not At All ○ A Little Bit ○ Somewhat ○ Quite A Bit ○ Very Much
8 1st Significant Issue Struggling with	(Free text response)
9 2nd Significant Issue Struggling with	(Free text response)
10 3rd Significant Issue Struggling with	(Free text response)

Appendix 5: Examples of dose intensity calculations

Example Olaparib dosing

The planned dosing schedule was 400mg twice daily (a total daily dose of 800mg per day).

RDI	PID	Patient	Study Day										
			1	2	3	4	5	6	7	8	9	10	11
100%	100%	1											P
100%	50%	2						D					P
50%	50%	3											P
70%	70%	4											P
57%	40%	5								D			P
	Received the total daily dose of 800mg												
	Dose reduction (less than 800mg; in this example 400mg)												
	Missed dose (0mg)												
D	Discontinuation IP												
P	Progression (or censoring event)												

Patients 1-5 progressed on Day 11, so the intended dose through to progression was 10 * 800 mg of olaparib = 8000 mg.

Patient 1 received a total dose of 8000mg of olaparib, whereas patients 2-5 received less treatment due to:

- Early stopping (Patient 2)
- Missed dose (Patient 3)
- Dose reduction and missed dose (Patient 4)
- Early stopping, missed doses and dose reductions (Patient 5)

Patient 1: RDI = PID = (10 * 800mg)/ 8000 mg = 100%

Patient 2: RDI = (5 * 800 mg)/ 4000 mg = 100%

PID = (5 * 800 mg)/ 8000 mg = 50%

Patient 3: RDI = PID = (5 * 800 mg)/ 8000 mg = 50%

Patient 4: RDI = PID = ((5 * 800 mg) + (4 * 400 mg))/ 8000 mg = 70%

Patient 5: RDI = ((3 * 800 mg) + (2 * 400 mg))/ 5600 mg = 57%

PID = ((3 * 800 mg) + (2 * 400 mg))/ 8000 mg = 40%