Statistical Analysis Plan

Study ID: 213358

Official Title of Study: A PHASE 2, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND EFFICACY OF NIRAPARIB COMBINED WITH BEVACIZUMAB AS MAINTENANCE TREATMENT IN PATIENTS WITH ADVANCED OVARIAN CANCER, FALLOPIAN TUBE CANCER, OR PRIMARY PERITONEAL CANCER FOLLOWING FRONT-LINE PLATINUM-BASED CHEMOTHERAPY WITH BEVACIZUMAB

Protocol 3000-02-004

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STATISTICAL ANALYSIS PLAN

A PHASE 2, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND EFFICACY OF NIRAPARIB COMBINED WITH BEVACIZUMAB AS MAINTENANCE TREATMENT IN PATIENTS WITH ADVANCED OVARIAN CANCER, FALLOPIAN TUBE CANCER, OR PRIMARY PERITONEAL CANCER FOLLOWING FRONT-LINE PLATINUM-BASED CHEMOTHERAPY WITH BEVACIZUMAB

Protocol 3000-02-004

Protocol Number:	3000-02-004
Protocol Version and Date:	Version 2.0: 05 December 2017 (Amendment 1) Version 1.0: 19 April 2017 (Original)
Study Drug Name:	Niraparib; Bevacizumab
Phase:	Phase 2
Methodology:	Open-Label, Single-Arm
Sponsor:	GSK/TESARO, Inc. 1000 Winter Street Waltham MA 02451 PPD GSK/TESARO UK, Limited 55 Baker Street London W1U7EU United Kingdom PPD
Sponsor Representative:	PPD , MD, PhD PPD
Analysis Plan Date:	08 Feb 2021
Analysis Plan Version:	Final Version 1.0

SPONSOR SIGNATURE PAGE

Protocol Title:	A Phase 2, Single-Arm, Open-Label Study to Evaluate the Safety and Efficacy of Niraparib Combined with Bevacizumab as Maintenance Treatment in Patients with Advanced Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer Following Front-Line Platinum-Based Chemotherapy with Bevacizumab
Protocol Number:	3000-02-004
Sponsor:	GSK/TESARO, Inc. 1000 Winter Street Waltham MA 02451 GSK/TESARO UK, Limited 55 Baker Street London W1U7EU United Kingdom

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Author:

PPD , PhD
PPD , Biostatistics

Signature: PPD

Date:_____

Approver:

PPD , MD, PhD
PPD

Signature:

Date:_____

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Table 1:   Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	activity of daily living
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
BER	base excision repair
BRCA	breast cancer susceptibility gene
CA-125	cancer antigen 125
CBC	complete blood count
CI	confidence interval
CR	complete response
CT	computed tomography
CVA	cerebrovascular accident
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ESMO	European Society for Medical Oncology
EU	European Union
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy–Ovarian Symptoms Index
g*BRCA*	germline breast cancer susceptibility gene
g*BRCA*mut	germline *BRCA* mutation
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Explanation
HR	hazard ratio
HRD	homologous recombination deficiency
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ICF	informed consent form
IV	intravenous
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NED	no evidence of disease
OAE	other adverse events
OS	overall survival
PARP	poly(ADP-ribose) polymerase
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PFS6	PFS rate at 6 months
PFS12	PFS rate at 12 months
PFS18	PFS rate at 18 months
PR	partial response
PRO	patient-reported outcome
QD	once daily
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
s*BRCA*	somatic *BRCA*
TEAE	treatment-emergent adverse event

Abbreviation or Specialist Term	Explanation
TFST	time to first subsequent therapy
TSST	time to second subsequent therapy
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

Homologous recombination deficiency (HRD) and dependency on neo-angiogenesis are 2 major vulnerabilities of human cancers that have been successfully exploited therapeutically, as evidenced by recent approvals of poly(ADP-ribose) polymerase (PARP) inhibitors including niraparib (Zejula®) for ovarian cancer and angiogenesis inhibitors including bevacizumab (Avastin®; Genentech/Roche United States [US]) for several indications including ovarian cancer. Emerging pre-clinical and clinical data suggest that combination of these 2 classes of agents may increase therapeutic options for women with ovarian cancer.

PARP-1 and PARP-2 are key enzymes for repairing single-strand deoxyribonucleic acid (DNA) breaks. When they are inhibited, single-strand DNA breaks become double-strand DNA breaks after DNA replication, forcing cancer cells to rely on double-strand break repair mechanisms, in particular homologous recombination, for survival and proliferation.

PARP inhibitors selectively kill a subset of cancer cells with deficiencies in DNA repair pathways. For example, a tumor arising in a patient with a germline breast cancer susceptibility gene mutation (g*BRCA*mut) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on base excision repair (BER), a pathway blocked by PARP inhibitors, for maintenance of genomic integrity.

Niraparib is an oral inhibitor of PARP-1 and PARP-2, which play a role in DNA repair. Niraparib is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who exhibit a complete response (CR) or partial response (PR) to platinum-based chemotherapy.

Bevacizumab is an antiangiogenic recombinant humanized monoclonal immunoglobulin G1 antibody against the vascular endothelial growth factor (VEGF) protein. Bevacizumab (Avastin®; Genentech/Roche US) has been approved in the US and European Union (EU) for the treatment of multiple tumor types in combination with certain other treatments. In the EU, bevacizumab is approved for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics [FIGO] Stages IIIB, IIIC, and IV) ovarian cancer. In the US, bevacizumab is approved for the treatment of patients with platinum-sensitive recurrent ovarian cancer, either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab as a single agent.

Recent data suggest that the combination of a PARP inhibitor, like niraparib, with a VEGF inhibitor, like bevacizumab, in maintenance treatment has the potential for improved PFS benefits after front-line chemotherapy in platinum-responsive (CR or PR) ovarian cancer patients. This hypothesis is supported by the mechanism of action of both treatments, nonclinical studies, and an ongoing Phase 1/2 study (AVANOVA) in this patient population. To date, the combination has proven to be safe for administration for extended periods in patients with advanced ovarian cancer.

Based upon the above preclinical and clinical data, the current study is being conducted to explore the safety and efficacy of maintenance with PARP inhibitor combined with anti-angiogenic agent following front-line, platinum-based therapy combined with bevacizumab.

1.1.2.   Study Objectives

The primary objective of this study is to evaluate the efficacy of niraparib in combination with bevacizumab, as assessed by 18-month progression-free survival (PFS) landmark analysis, in patients with Stage IIIB to IV ovarian cancer who have CR, PR, or no evidence of disease (NED) following front-line, platinum-based chemotherapy with bevacizumab.

The secondary objectives include the following:

- To evaluate additional measures of clinical benefit, including PFS, RECIST or CA-125 progression-free survival, OS, patient-reported outcome (PRO) measures, TFST, and time to second subsequent therapy (TSST)

- To evaluate the safety and tolerability of niraparib and bevacizumab combination in the indicated target population

The exploratory objectives include the following:

- To evaluate PFS rate at 6 months (PFS6) and 12 months (PFS12)

- Retrospective analysis to evaluate HRD per the Myriad myChoice® HRD test as a potential biomarker for response to the niraparib and bevacizumab combination

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analyses of study data in order to answer the study objectives. Patient populations to be used for analyses, data handling rules, statistical methods, and formats for data presentation are identified and provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

The SAP is based upon Study Protocol v2.0 dated 05 December 2017

1.2.   Study Design

Synopsis of Study Design

This is a multicenter, Phase 2, single-arm, open-label study to evaluate niraparib combined with bevacizumab as maintenance treatment in patients with advanced (Stage IIIB-IV) ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with completely or incompletely resected disease who are recovered from primary debulking surgery.

Approximately 90 patients will be enrolled.

Eligible patients who achieve CR, PR, or NED following treatment with platinum-based chemotherapy in addition to bevacizumab will be enrolled in the study and receive maintenance treatment with niraparib (for up to 3 years) combined with bevacizumab (for up to 10 months during the maintenance phase or up to a total of 15 months inclusive of the approximately 5 months of bevacizumab received with chemotherapy) or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death, whichever comes first (see Study Design Schema). Patients who have not progressed after 3 years of niraparib maintenance treatment will be given the option to continue with niraparib beyond 3 years if they are tolerating and benefiting from treatment and after consultation with the Sponsor.

Study Design Schema
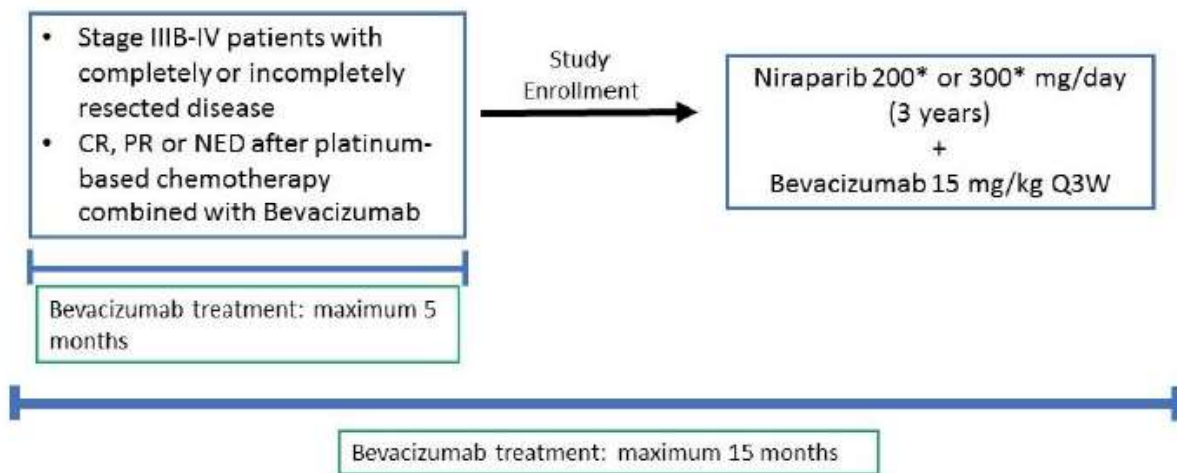
Abbreviations: CR = complete response; NED = no evidence of disease; PR = partial response.
*Patients ≥77 kg **and** with platelet count of ≥150,000/µL will receive 300 mg/day; patients <77 kg **and/or** with platelet count of <150,000 u/L will receive 200 mg/day

Safety assessments conducted throughout the treatment period include treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), treatment discontinuations or dose reductions due to adverse events (AEs), changes in Eastern Cooperative Oncology Group (ECOG) performance status, changes in clinical laboratory results (hematology and chemistry), vital sign measurements, observations during physical examination, and use of concomitant medications.

Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 tumor assessment via computed tomography (CT) or magnetic resonance imaging (MRI) scan of the abdomen/pelvis and clinically indicated areas is required at screening, then every 12 weeks (±7 days) from Cycle 1/Day 1 visit for the first 48 weeks, then every 24 weeks (±14 days) until disease progression, at which point a final follow-up set of imaging scans is required. Positron emission tomography (PET)/CT may be used according to RECIST v1.1 guidelines, but its use is not a study requirement.

Tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, scans should continue at the specified intervals.

RECIST v1.1 is used to define progressive disease (PD) in this study. Tumor assessment by CT/MRI must unequivocally show PD according to RECIST v1.1 criteria. PD will not be diagnosed in case of CA-125 progression in the absence of radiologic evidence of progressive disease.

If a patient had a CT/MRI of the abdomen/pelvis and clinically indicated areas within the 28-day screening window before Cycle 1/Day 1 but prior to signing the main informed consent form (ICF), the patient is not required to complete an additional CT/MRI scan for study screening.

PROs (Functional Assessment of Cancer Therapy-Ovarian Symptom Index [FOSI]) will be collected every 6 weeks (±7 days) for 6 months, then every 12 weeks (±7 days) thereafter while the patient is receiving study treatment. Once a patient discontinues treatment, PRO evaluations will be performed 4 weeks (±7 days), 8 weeks (±7 days), 12 weeks (±7 days), and 24 weeks (±7 days) after treatment discontinuation, regardless of subsequent treatment.

All patients will undergo an End of Treatment Visit within 7 days of the decision to discontinue treatment for any reason. Post-treatment follow-up visits will be conducted every 12 weeks (±14 days) after the last dose of study treatment.

All AEs and SAEs, regardless of causality, will be collected and recorded for each patient from the day the ICF is signed until 90 days after the last dose of study treatment. Any pregnancies that occur within 180 days post-treatment are to be reported. All AEs and SAEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the change(s) observed, until the patient is lost to follow-up or withdraws consent, or until the patient has died.

The adverse events of special interest (AESIs) for this study are myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), pneumonitis, embryo-fetal toxicity, and secondary cancer (new malignancies other than MDS/AML). AESIs must be reported to the Sponsor as soon as the Investigator becomes aware of them or within 24 hours.

1.2.1.   Randomization Methodology

Not applicable as this is a single-arm study.

1.2.2.   Stopping Rules and Unblinding

There are no pre-specified stopping rules for the study. Unblinding is not applicable as this is a single-arm, open-label study.

1.2.3.   Study Procedures

The schedule of events, as outlined in the study protocol, is provided in Table 2

Table 2: Schedule of Events

Visit/Procedure	Screening	Cycle 1[a]	Cycle 2[a]	Subsequent cycles[a]	EOT[b]	Post-treatment assessments
Day	-28 to -1	1	1	C(n)/D1	Within 7 days of the decision to discontinue treatment	Every 12 weeks
Visit Window		±3 days	±3 days	±3 days		±14 days (unless otherwise specified)
Informed consent	X					
Demographics and height	X					
Medical, surgical, cancer (including genotyping), and medication history	X					
Medical history/concomitant medications		X	X	X	X	
Sample collection (tumor) for HRD testing[c]	X					
12-lead ECG	X					
Serum or urine pregnancy test[d]	X[d]	X	X	X	X	
Physical examination	X	X	X	X	X	
Vital signs and weight	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	
CBC[e]	X	Days 1, 8, and 15 of Cycle 1[f] and Cycle 2		X	X	
Serum chemistry and coagulation	X	X[f]	X	X	X	

Visit/Procedure	Screening	Cycle 1[a]	Cycle 2[a]	Subsequent cycles[a]	EOT[b]	Post-treatment assessments
Day	**-28 to -1**	**1**	**1**	**C(n)/D1**	**Within 7 days of the decision to discontinue treatment**	**Every 12 weeks**
Visit Window		**±3 days**	**±3 days**	**±3 days**		**±14 days (unless otherwise specified)**
Urinalysis	X					
Urine sample for protein[g]	X	X[g]	X[g]	X[g]		
Serum CA-125	X	X	X	X	X	X
RECIST v1.1 assessment[h]	X			X[h]	X	X
Chest CT or MRI[i]	X					
PRO	X	Q6W (±7 days) for 6 months, then Q12W (±7 days)			4, 8, 12, and 24 weeks (±7 days) after last dose	
Niraparib dispensed or collected		X	X	X	X	
Bevacizumab infusion		X	X	X		
Adverse event monitoring[j]	X	X	X	X	X	X
Anticancer therapies assessment						X
Survival assessment (telephone assessment allowed)[k]						X
Bone marrow aspirate and biopsy		For any suspected case of MDS/AML or secondary cancer (new malignancy other than MDS/AML) reported while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist.				

Abbreviations: AE = adverse event; AML = acute myelogenous leukemia; C = cycle; CA-125 = cancer antigen 125; CBC = complete blood count; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FOSI = Functional Assessment of Cancer Therapy–Ovarian Symptom Index; HRD = homologous recombination deficiency; MDS = myelodysplastic syndrome; MRI = magnetic resonance imaging; PE = physical examination; QxW = every x weeks; RECIST = Response Evaluation Criteria in Solid Tumors

[a] Treatment cycles are 21 days (±3 days) long.

[b] EOT is defined as the discontinuation of treatment for any reason.

[c] The tumor sample must be confirmed to be available during the screening period and submitted after the patient has been enrolled; patients do not have need to wait for the HRD test result to be enrolled. If archival tumor tissue is not available for testing, the patient must agree to undergo a fresh biopsy.

[d] For patients of childbearing potential only. If completed within 72 hours of the first dose, pregnancy testing does not need to be repeated.

[e] If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC will also be required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume.

[f] Screening assessments completed within 7 days of the first dose do not need to be repeated, unless otherwise specified.

[g] Urine dipstick for protein determination should be performed prior to each bevacizumab administration. Patients discovered to have ≥ 2 proteinuria on dipstick should not be administered bevacizumab, should undergo a 24-hour urine collection, and must demonstrate < 2 g of protein in 24 hours to be eligible for bevacizumab treatment to resume.

[h] RECIST v1.1 tumor assessment via CT or MRI scan of the abdomen/pelvis and clinically indicated areas required at screening, every 12 weeks (±7 days) from Cycle 1/Day 1 for the first 48 weeks, then every 24 weeks (±7 days) until disease progression, at which point a final follow-up set of imaging is required.

[i] Chest CT or MRI if not done as part of RECIST tumor assessment. If the chest CT or MRI is clear at screening, repeat chest imaging is not required in the absence of lesions to be followed or in the absence of clinical indication requiring follow-up; otherwise, repeat chest imaging should be completed at the same time as RECIST imaging.

[j] All AEs and SAEs, regardless of causality, will be collected and recorded for each patient from the day the ICF is signed until 90 days (±14 days) after the last dose of study treatment or until alternate anticancer therapy has been initiated, whichever occurs first.

[k] Patients will be followed until study closeout for survival status and study-drug related SAEs.

1.2.4.   Efficacy, Pharmacokinetic, and Safety Parameters

1.2.4.1.   Efficacy Parameters

Protocol-specified efficacy parameters include:

- PFS rate at 18 months (PFS18), which is defined as the proportion of patients who have not progressed or died within 18 months after niraparib combined with bevacizumab treatment initiation. Progression will be assessed by RECIST v1.1 criteria per Investigator assessment.

- PFS, which is defined as the time from niraparib combined with bevacizumab treatment initiation to the earlier date of assessment of progression, as assessed by RECIST v1.1 criteria, based on Investigator assessment, or death by any cause in the absence of progression.

- OS, which is defined as the date of initiation of niraparib treatment in combination with bevacizumab to the date of death by any cause.

- RECIST or CA-125 progression-free survival, which is defined as the time from initiation of niraparib treatment in combination with bevacizumab to the earliest date of progression assessed by RECIST v1.1. or CA-125 progression or death by any cause.

  The date of CA-125 progression will be the date of the first measurement that meets the CA-125 progression criteria: Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 $\geq 2 \times$ ULN on 2 occasions at least 1 week apart, OR

  - Patients with elevated CA-125 pretreatment that never normalizes must show evidence of CA-125 $\geq 2 \times$ the nadir value on 2 occasions at least 1 week apart, OR

  - Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 $\geq 2 \times$ ULN on 2 occasions at least 1 week apart.

- TFST (Time to First Subsequent Therapy), which is defined as the date of initiation of niraparib treatment in combination with bevacizumab treatment in the current study to the start date of the first subsequent anticancer therapy.

- TSST (Time to Second Subsequent Therapy), which is defined as the date of initiation of treatment of niraparib in combination with bevacizumab treatment in the current study to the start date of the second subsequent anticancer therapy.

- Observed changes from baseline in the Functional Assessment of Cancer Therapy–Ovarian Symptom Index (FOSI) PRO will be assessed (see Appendix 7.1).

The exploratory efficacy endpoints are PFS rate at 6 months (PFS6) and 12 months (PFS12), which are defined as the proportion of patients who have not progressed or died within 6 months and 12 months after initiation of treatment of niraparib in combination with bevacizumab treatment, respectively. Progression will be assessed by RECIST v1.1 Criteria based on Investigator assessment. Additional landmark PFS analyses may be performed as deemed appropriate.

1.2.4.2.   Pharmacokinetic Parameters

No PK samples are collected in this study.

1.2.4.3.   Safety Parameters

Safety will be evaluated based on the incidence of TEAEs, serious adverse events (SAEs), treatment discontinuations or dose modifications due to AEs, changes in ECOG performance status, changes in clinical laboratory results (hematology and chemistry), vital sign measurements, observations during physical examination, and use of concomitant medications. All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) coding system. The safety endpoints are:

- TEAEs
- Clinical laboratory:
    - Complete blood count (CBC): hemoglobin, WBC (Leukocytes), mean corpuscular volume, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes, and platelet count.
    - Serum chemistry: albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen, calcium, chloride, creatinine, glucose, magnesium, potassium, sodium, total protein and urea.
    - Urinalysis: Bilirubin, Glucose, Ketones, Leukocyte esterase, Nitrites, Occult Blood, Urobilinogen, and Specific gravity.
    - Urine Protein
    - Serum or Urine pregnancy testing
- Vital signs:
    - Height
    - Weight
    - Temperature
    - Systolic Blood Pressure
    - Diastolic Blood Pressure
    - Pulse
- ECOG performance status
- ECG (Standard 12-lead electrocardiograms at screening)
- Concomitant medications

Additional safety parameters include study treatment exposure and compliance.

2. PATIENT POPULATION

2.1. Population Definitions

The following patient populations will be evaluated and used for presentation and analysis of the data:

- Safety population: All patients who receive any amount of study treatment (ie, any amount of bevacizumab or niraparib during the study). All safety endpoints will be assessed in the safety population.

- Efficacy population: All patients who receive any amount of niraparib (at least 1 dose). The primary analysis of efficacy endpoints will be performed on the efficacy population.

- Per-protocol population: All patients in the efficacy population who have no major protocol violations during the study and have at least 1 protocol-required postbaseline tumor assessment.

Given the single arm study design, the safety population will be used to summarize the patient disposition and baseline characteristics in this study. The efficacy population, which is the ITT (intent-to-treat) population in this study, is the primary population for the analysis of efficacy endpoints. The safety population is the primary population for the analysis of safety endpoints. The patients in the Per-protocol population are subjects that have neither GSK important nor Tesaro significant protocol deviations and have at least 1 protocol-required postbaseline tumor assessment. The Per-protocol population will be used in supportive analyses when applicable.

2.2. Protocol Deviations

2.2.1. GSK definitions

A protocol deviation is any failure to comply with the study protocol as approved by the relevant regulatory authority, ethics committee and/or institutional review board, whether planned or unplanned. Protocol Deviations will be assessed as important per Sponsor's SOP (SOP_00000130050 – 4.0).

GSK Important protocol deviations are those deviations which directly or indirectly have an impact on:

- subject's rights, safety, or well-being, and/or on
- data integrity and/or
- Regulatory compliance, as per ICH E3.

Examples per ICH E3 include:

- Subjects who are entered into the study even though they did not satisfy key entry criteria. [ICH E3 10.2]

- Subjects who developed withdrawal criteria during the study but were not withdrawn. [ICH E3 10.2]

- Subjects who received the wrong treatment or incorrect dose. [ICH E3 10.2]

- Subjects who received an excluded concomitant treatment. [ICH E3 10.2]
- Any study specific procedure or assessment deviation, which the study team determines may compromise subject rights, safety, or well-being, or has a significant impact on study conclusions.

2.2.2. Tesaro definitions

A protocol deviation is any failure to comply with the study protocol as approved by the relevant regulatory authority, ethics committee and/or institutional review board, whether planned or unplanned.

A protocol deviation is classified as a Tesaro important protocol deviation if there is the potential to:

- Impact the completeness, accuracy, and/or reliability of the study data, or
- Affect a subject's rights, safety, or well-being.

Tesaro important protocol deviations require review to confirm whether or not they are significant. The following are PDs that will always be considered important (SOP 1000-00021-CLN):

- Failure to obtain informed consent for participation in the clinical trial
- Enrollment of ineligible subject
- Subject developed withdrawal criteria during the study but was not withdrawn
- Subject received incorrect treatment (patient received non-study drug to treat ovarian cancer)
- Incorrect or non-compliant dosing of a subject, i.e. dosing that is inconsistent with the protocol
- Administration of an excluded concomitant treatment to a trial subject

A protocol deviation is classified as a Tesaro significant PD if it has been confirmed to:

- Adversely impact the completeness, accuracy, and/or reliability of the study data
- Affect a subject's rights, safety, or well-being.

2.2.3. Deviation Analyses

All protocol deviations will be identified and finalized prior to database lock. Patients excluded from the Per-protocol population due to either a GSK important or a Tesaro significant protocol deviation will be identified prior to database lock.

The following protocol deviation summaries will be provided:

- Summary of GSK Important Protocol Deviations not related to COVID-19 (ITT)
- Summary of GSK Important Protocol Deviations related to COVID-19 (ITT)
- Summary of Tesaro Significant Deviations related to COVID-19 (ITT)

- Summary of Tesaro Significant Deviations not related to COVID-19 (ITT)
- Listing of GSK Protocol Deviations not related to COVID-19 (ITT)
- Listing of GSK Protocol Deviations related to COVID-19 (ITT)
- Listing of Tesaro Protocol Deviations not related to COVID-19 (ITT)
- Listing of Tesaro Protocol Deviations related to COVID-19 (ITT)

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

The sample size of the study is driven by the primary endpoint: PFS18. A sample size of 90 patients will provide an 11% precision on the 95% exact CI of PFS18, assuming a true PFS18 rate of 48%, which corresponds to a median PFS of 17 months based on exponential PFS assumption. The primary endpoint analysis will occur after approximately 3 months of enrollment and an additional 18 months of follow-up.

3.2. General Methods

All safety data listings that contain an evaluation date will also contain a relative study day. Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study drug which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. The last day of study drug is designated with an "L" (eg, Day 14L). Post-treatment study days are numbered relative to the last dose and are designated as Day +1, Day +2, etc. In addition to relative day, cycle and day of treatment within cycle will be calculated and presented.

All output will be incorporated into Microsoft Word or Excel files or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters.

For categorical variables, summary tabulations of the number and percentage of patients within each category of the parameter will be presented. Percentages will be based on the patients with a non-missing parameter. Percentages will be reported to 1 decimal place. Percentages will not be presented for zero counts.

For continuous variables, the number of patients, mean, standard deviation (SD), median, first quartile (Q_1), third quartile (Q_3), minimum, and maximum values will be presented.

Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations.

No formal statistical hypothesis testing will be performed.

In addition:

- P-values greater than or equal to 0.001, in general, will be presented to 3 decimal places; p-values less than 0.001 will be presented as "<0.001"
- CIs will be presented to 1 more decimal place than the raw data
- Weeks will be calculated as Number of days divided by 7
- Months will be calculated as Number of days divided by 30.4375
- Years will be calculated as Number of days divided by 365.25
- Day 1 will be considered as the first day of treatment
- End of Study is defined as the last available study assessment

- All tables, figures, and listings will include footers at the bottom of the page reflecting the path and date of the datasets, datasets used to generate the tables, figures, and listings, and date and time of the generation of the output

3.3. Computing Environment

All statistical analyses will be performed using SAS statistical software v9.4 or later, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v20.0 or later. Laboratory parameter changes will be described using shift tables, relative to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Concomitant medications will be coded using the latest version of the World Health Organization's (WHO) Anatomical Therapeutic Chemical (ATC) classification.

3.4. Baseline Definitions

For all analyses, baseline is defined as the most recent measurement prior to the first administration of study drug (including Cycle 1 Day 1).

3.5. Methods of Pooling Data

Data will be pooled across study sites.

3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned for the efficacy or safety endpoints.

3.7. Multiple Comparisons/Multiplicity

Not applicable.

3.8. Subpopulations

3.8.1. Study Subpopulations

- Best response during front-line platinum regimen (CR/NED or PR)
- Age categories [<65 or ≥65]
- ECOG status [0 or 1]
- Stage of disease at initial diagnosis [III or IV]
- Neoadjuvant vs Adjuvant chemotherapy during front-line platinum regimen
- Macroscopic visible residual disease after surgery [Yes, No or unknown]

3.8.2. Biomarker Subpopulations

3.8.2.1. Biomarker Definitions

Germline BRCA mutation (gBRCAmut): An inherited deleterious or suspected deleterious mutation in either a BRCA1 or BRCA2 tumor suppressor gene found in blood.

BRCA mutation (BRCAmut): A deleterious or suspected deleterious BRCA1 or BRCA2 mutation found in a tumor.

BRCA wild type (BRCAwt): A tumor does not possess either a deleterious or suspected deleterious BRCA mutation.

Homologous recombination deficiency (HRD): Dysregulation in the homologous recombination pathway (due to genetic mutations or alterations) leading to cellular genomic instability and an inability to efficiently repair damaged DNA.

HRD positive (HRDpos): HRD positive status may be determined by the myChoice HRD test. Any tumor that scores ≥42 or has a deleterious or suspected deleterious BRCA mutation would be considered HRD positive.

HRD negative (HRDneg): HRD negative status may be determined by the myChoice HRD test. Any tumor that scores <42 and does not possess a deleterious or suspected deleterious BRCA mutation would be considered HRD negative.

3.8.2.2.   Study-Specific Biomarker Populations

In this study, BRCA and HRD status are determined by tumor samples at screening via the Myriad myChoice HRD test. The gBRCA status is recorded in the eCRF form.

All patients will be summarized by BRCA status as follows:

- BRCAmut
- BRCAwt
- Not determined

All patients will be summarized by HRD status in the following subgroups:

- HRDpos

    o   HRDpos/BRCAmut
    o   HRDpos/BRCAwt

- HRDneg
- Not determined

If applicable, other exploratory biomarker subpopulations may be further defined and analyzed.

3.8.3.   Other Study-Specific Subpopulations

Starting dose of study medication will be determined for each newly enrolled patient based on baseline weight and platelet count. The following subpopulations are defined for subgroup analysis when applicable.

- Starting dose 200 mg/day (Recommended for patients with baseline weight < 77kg and/or baseline platelet count < 150,000/μL)
- Starting dose 300 mg/day (Recommended for patients with baseline weight ≥ 77kg and baseline platelet count ≥ 150,000/μL)

3.9.   Withdrawals, Dropouts, Loss to Follow-up

Patients who are withdrawn or discontinue from the study will not be replaced.

3.10.   Missing Data

In general, there will be no substitutions made to accommodate missing data points. Methods for handling incomplete PRO instruments are performed according to their scoring manuals. All data recorded on the eCRF will be included in data listings that will accompany the CSR.

When tabulating AE data, partial dates will be handled as follows.

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment.

- If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent.

- A missing onset date will be coded as the day of treatment. If the resulting onset date is after a reported date of resolution, the onset date will be set equal to the date of resolution.

- Imputation of partial dates is used only to determine whether an event is treatment-emergent; data listings will present the partial date as recorded in the eCRF.

3.11.   Visit Windows

It is expected that all visits should occur according to the protocol schedule. By-visit summaries and analyses will be by nominal visit (all data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window for analysis). In data listings, the relative day of all dates will be presented.

For PRO endpoints, visit windows will be applied to PRO assessments after EOT as shown in Table 3 when applicable. If multiple assessments are observed in a window, the visit closest to the scheduled assessment date will be used. If equally close, the earlier visit will be used.

Table 3:   Windows (Inclusive) for PRO Assessments after EOT

Visit after EOT	Scheduled Day after EOT	Window (Days)
4 weeks	28	14 to 42
8 weeks	56	43 to 70
12 weeks	84	71 to 126
24 weeks	168	127 to 210

3.12. Interim Analyses

No formal interim analysis is planned.

4.   STUDY ANALYSES

4.1.   Patient Disposition

Patient disposition will be tabulated and include the numbers of screened patients (who have signed informed consent), the numbers who discontinued treatment and discontinued study and reason(s) for withdrawal, and the number of patients who died.

A by-patient data listing of study completion information including the reasons for treatment discontinuation and/or study discontinuation will be presented.

4.2.   Demographics, Baseline Characteristics, and Medical History

Demographics, baseline characteristics, and medical history information will be summarized using descriptive statistics. No formal statistical comparisons will be performed.

Demographic and baseline data for each patient will be provided in data listings.

The demographic and baseline characteristics tables will include the following variables:

- Age at time of screening (years) calculated as date of screening minus date of birth / 365.25, unless local regulations prevent the collection of date of birth, in which case age, as reported on the eCRF, will be used

- Age categories (18 to <65, 65 to <75, $\geq$75; and $\geq$65)

- Race (White, Black or African American, Asian, American Indian/Alaska native, native Hawaiian or other Pacific Islander, and other)

- Ethnicity (Hispanic, non-Hispanic, unknown, and not reported)

- Time from first diagnosis to first dose (years)

- Primary tumor site (ovarian, primary peritoneal, or fallopian tube)

- International Federation of Gynecology and Obstetrics (FIGO) stage at time of initial diagnosis

- Baseline weight (in kilograms, last value prior to first dose; if weight is reported in pounds, convert to kilograms by dividing by 2.2)

- Baseline height (in centimeters, last value prior to first dose; if height is reported in inches, convert to centimeters by multiplying by 2.54)

- Baseline body mass index (BMI) (kg/m^2), calculated using the patient's height and weight at Baseline [BMI (kg/m^2) = weight (kg) / height $(m)^2$]

- ECOG performance status at baseline

- Baseline CA-125 level

- Baseline platelet count

- History of myelosuppression (thrombocytopenia, leukopenia, anemia, or neutropenia)

- History of blood transfusion and growth factors

- Prior ovarian cancer treatment and surgery

- Ovarian cancer pathology

- BRCA and HRD status by Myriad myChoice® HRD test

Medical history will be coded using MedDRA v20.0 or later, and the number and percentage of patients experiencing at least 1 such diagnosis by MedDRA System Organ Class (SOC) and preferred term (PT) will be reported.

Prior and follow-up anti-cancer therapy will be summarized according to Table 4 when applicable.

Table 4:   Reported Anti-cancer Therapies

Therapy	Regimens (Preferred Terms)
Platinum	CARBOPLATIN CARBOPLATIN W/GEMCITABINE CARBOPLATIN W/PACLITAXEL CISPLATIN CISPLATIN W/DOXORUBICIN CISPLATIN W/PACLITAXEL OXALIPLATIN PACLITAXEL W/CARBOPLATIN
Carboplatin	CARBOPLATIN CARBOPLATIN W/GEMCITABINE CARBOPLATIN W/PACLITAXEL PACLITAXEL W/CARBOPLATIN
Cisplatin	CISPLATIN CISPLATIN W/DOXORUBICIN CISPLATIN W/PACLITAXEL
Taxane	DOCETAXEL ABRAXANE PACLITAXEL PACLITAXEL ALBUMIN PACLITAXEL W/CARBOPLATIN CARBOPLATIN W/PACLITAXEL CISPLATIN W/PACLITAXEL
Doxorubicin	DOXORUBICIN DOXORUBICIN HYDROCHLORIDE LIPOSOMAL DOXORUBICIN HYDROCHLORIDE PEGYLATED LIPOSOMAL DOXORUBICIN PEGYLATED LIPOSOMAL DOXORUBICIN HYDROCHLORIDE CYCLOPHOSPHAMIDE W/DOXORUBINCIN CISPLATIN W/DOXORUBICIN
Gemcitabine	GEMCITABINE GEMCITABINE HYDROCHLORIDE CARBOPLATIN W/GEMCITABINE CARBOPLATIN W/GEMCITABINE HYDROCHLORIDE CISPLATIN W/GEMCITABINE HYDROCHLORIDE

Pemetrexed	PEMETREXED
Topotecan	TOPOTECAN
Mirvetuximab Soravtansine	MIRVETUXIMAB SORAVTANSINE
Bevacizumab	BEVACIZUMAB
Cyclophosphamide	CYCLOPHOSPHAMIDE CYCLOPHOSPHAMIDE W/DOXORUBINCIN
PARP inhibitor	OLAPARIB NIRAPARIB RUCAPARIB RUCAPARIB CAMSYLATE TALAZOPARIB VELIPARIB
PD(L)-1 inhibitor	PEMBROLIZUMAB ATEZOLIZUMAB DURVALUMAB NIVOLUMAB AVELUMAB CEMIPLIMAB

4.3.   Efficacy Evaluation

All analyses will include summary statistics, including number and percentage for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using Kaplan-Meier methodology. Two-sided 95% CIs will be provided where appropriate. Subgroups will also be analyzed for the primary efficacy endpoint based on age, ECOG, disease stage, HRD and BRCA status, neoadjuvant vs adjuvant, macroscopic visible residual disease after surgery, and best response to first-line platinum regimen. No formal statistical testing will be performed.

4.3.1.   Primary efficacy analyses

The primary efficacy endpoint is PFS rate at 18 months (PFS18), which is defined as the proportion of patients who have not progressed or died within 18 months after niraparib combined with bevacizumab treatment initiation. Progression will be assessed by RECIST v1.1 criteria per Investigator assessment. For the primary analysis, PFS18 will be estimated by

- Number of ITT patients without documented progression or death by month of 18 divided by number of ITT patients

The 95% exact confidence interval will also be provided.

In addition, the probability of PFS at 18 months will be estimated using the Kaplan-Meier method by.

The following subgroup analyses will be performed for PFS18 and PFS:

- Age categories [<65 or ≥65]

- ECOG status [0 or 1]

- Stage of disease at initial diagnosis [III or IV]

- HRD status [HRDpos, HRDpos/BRCAmut, HRDpos/BRCAwt, HRDneg, or Not determined]

- BRCA status [BRCAmut, BRCAwt, or Not determined]

- Neoadjuvant vs Adjuvant chemotherapy during front-line platinum regimen

- Macroscopic visible residual disease after surgery [Yes, No or unknown]

- Best response during front-line platinum regimen [CR/NED, or PR]

4.3.2. Secondary Efficacy Variables

4.3.2.1. Time to Event Endpoints

The time to event endpoints (PFS, OS, RECIST or CA-125 PFS, TFST, TSST) will be analyzed using Kaplan-Meier methodology. Expect for the RECIST or CA-125 PFS that progression will be based on either RECIST v1.1 or CA-125, the progression in other endpoints will be based on RECIST v1.1 only.

Quartiles (i.e., 25th percentile, median, 75th percentile) and associated 95% CIs from Brookmeyer and Crowley method with log-log transformation for event time will be estimated from the product-limit (KM) method. The KM estimate of the survival distribution function (SDF) will be computed. Estimates of the SDF will be presented at 6 months, 12 months, 18 months, 24 months, and so on as data allow. Kaplan-Meier plots of the SDF will be presented and will include the number of patients at risk over time. Summaries of the number and percentage of subjects experiencing an event, and the type of event will also be provided.

For PFS analysis, the following censoring rules will apply:

1. No evaluable baseline or post-baseline radiological tumor assessments, and no death or progression occurred within the two consecutive radiological tumor assessment intervals following the first dose (25-weeks time frame): censored at the first dose date

2. Start of subsequent anti-cancer therapy without a prior progression: censored at the date of last evaluable radiological tumor assessment on or prior to the start date of subsequent anti-cancer therapy, or the first dose date (whichever is later).

3. No progression or death and no subsequent anti-cancer therapy: censored at the date of last evaluable radiological tumor assessment or the first dose date (whichever is later)

4. Progression or death after two or more consecutive missing radiological assessments: censored at the date of last evaluable radiological tumor assessment prior to the consecutive missing assessments or the first dose date (whichever is later)

5. Progression or death: event (whichever is earlier)

For RECIST or CA-125 PFS, the following censoring rules will apply:

1. No evaluable baseline or post-baseline radiological tumor assessment, and no death or progression based on either RECIST v1.1 or CA-125 occurred within the two consecutive radiological tumor assessment intervals following the first dose (25 weeks time frame): censored at the first dose date

2. Start of subsequent anti-cancer therapy without a prior progression based on either RECIST v1.1 or CA-125: censored at the date of last evaluable radiological tumor assessment or CA-125 assessment on or prior to the start date of subsequent anti-cancer therapy, or the first dose date (whichever is later).

3. No progression based on either RECIST v1.1 or CA-125, or death and no subsequent anti-cancer therapy: censored at the date of last evaluable radiological tumor or CA-125 assessment, or the first dose date (whichever is later)

4. Progression based on either RECIST v1.1 or CA-125, or death after two or more consecutive missing radiological assessments and CA-125 assessment: censored at the date of last evaluable radiological tumor or CA-125 assessment prior to the consecutive missing assessments, or the first dose date (whichever is later)

5. Progression based on either RECIST v1.1 or CA-125, or death: event (whichever is earlier)

For TFST analysis, the following censoring rule will apply:

1. Any patient not known to have died at the time of analysis and not known to have had started the first line subsequent anti-cancer therapy will be censored at the last known time to have not received any subsequent therapy, i.e. the last assessment where this was confirmed.

2. Start of the first line subsequent anti-cancer therapy or death: event (whichever is earlier)

For TSST analysis, the following censoring rule will apply:

1. Any patient not known to have died at the time of analysis and not known to have had started any second line subsequent anti-cancer therapy will be censored at the last known time to have not received any second line subsequent therapy, i.e. the last assessment where this was confirmed.

2. Start of the second line subsequent anti-cancer therapy or death: event (whichever is earlier)

For OS, if no death: censored at the last date that patient was known to be alive.

4.3.2.2.   Patient Reported Outcomes

FOSI will be collected every 6 weeks (± 7 days) for 6 months, then every 12 weeks (± 7 days) thereafter while the patient is receiving study treatment. Once a patient discontinues treatment, FOSI evaluations will be performed 4 weeks (± 7 days), 8 weeks (± 7 days), 12 weeks (± 7 days), and 24 weeks (± 7 days) after treatment discontinuation, regardless of subsequent treatment.

FOSI may be completed remotely. It is estimated that FOSI evaluations will take less than 20 minutes at each timepoint. Since these are questionnaires, their completion will not interfere with or prevent future treatment or clinical studies. FOSI evaluations should be administered prior to conducting any other procedures at each visit.

The FOSI is a validated 8-item measure of symptom response to treatment for ovarian cancer. Patients respond to their symptom experience over the past 7 days using a 5-point Likert scale scored from CCI to CCI .

The FOSI score will be derived in accordance with the FOSI scoring manual (Appendix 7.2). Negatively stated items are reversed by subtracting the response from CCI . After reversing proper items, all subscale items are summed to a total. A higher score indicates a better Quality of Life (QOL).

If there are missing items, subscale scores will be prorated as long as more than 50% of the items were answered (i.e. at least 5 of 8 items). The proration is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered.

FOSI score = CCI / CCI

Summary statistics for observed FOSI score and changes from baseline at each post baseline visit will be provided. A mixed-effects model for repeated measures (MMRM) will be used to model the FOSI score changes over time. Least squares means and 95% CIs at each post baseline visit will be presented. Least squares means and standard error bars will be plotted over time. The analysis visits include baseline, post baseline visits, unless there is excessive missing data at a visit (defined as >75% missing data).

The MMRM model via PROC MIXED will include FOSI score changes from baseline at post baseline scheduled visits from week 6 (Cycle 3 Day 1) through EOT and up to 24 weeks after EOT (Follow-Up Week 24) as dependent variables; post baseline visit as fixed effect; baseline FOSI score as a continuous covariate along with the baseline-by-visit interaction; and subject as a random effect. An unstructured covariance matrix will be used to model the within subject variance and the Kenward-Roger approximation will be used to estimate the degrees of freedom. Restricted maximum likelihood (REML) estimation will be used. An overall least squares means estimate will be derived, representing the average treatment effect over visits giving each visit equal weight. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be used in order until convergence is reached: toeplitz with heterogeneity (TOEPH), autoregressive with heterogeneity (ARH(1)), Toeplitz (TOEP), and autoregressive (AR(1)). If there are still issues with the fit of the model or estimation of the treatment effects, SUBJECT will be treated as a fixed effect.

The FOSI categorical variables defined according to the minimum clinically important difference (MCID) levels will be summarized by visit. The FOSI score ranges from CCI CCI to CCI . A change of 2 points in FOSI score is considered as a MCID. The FOSI score change from baseline will be categorized at each post baseline visit as follows:

- Improved: change from baseline ≥ 2
- Stable: -2 < change from baseline < 2

- Worsened: change from baseline ≤ -2 or "Patient was too ill" is answered as the reason for not completing the FOSI form at visit.

In the reporting of the proportion of patients who have a response of Improved, Stable, or Worsened, the denominator will be all patients with non-missing FOSI scores at baseline and at each corresponding post baseline visit.

The Time to symptom worsening in FOSI score will be defined as the time from the date of first study dose date to the date of first worsened FOSI score (change from baseline ≤ -2).

Any patient without a worsened FOSI score will be censored at the date of the last evaluable FOSI assessment, i.e. FOSI score is not missing. Patients who have no valid baseline FOSI assessment or any post baseline FOSI assessment will be censored at the date of first study dose date.

The overall compliance and compliance by visit will be summarized, based on the following definitions.

- Expected forms: number of patients expected to complete PRO form. Date of study discontinuation and/or date of death will be used to determine the last visit at which a patient is still expected under PRO follow-up.

- Received forms: number of PRO forms received back.

- Evaluable forms: number of Received forms with at least one non-missing scale value plus number of forms not received back for reasons of "Patient was too ill".

The overall compliance rate is defined as the number of patients with an evaluable baseline and at least one evaluable post-baseline form, divided by the number of patients expected to complete the baseline form.

Compliance by visit will be calculated as the number of patients with an evaluable form at that visit, divided by the number of patients expected to complete the form at that visit.

The distribution of forms received and the reasons for forms not received back will be reported at each visit. To ensure the representativeness of the reported PRO data, a comparison of baseline characteristics for compliant vs. non-compliant patients may be performed if compliance is considered inadequate.

Descriptive summaries of individual items in each questionnaire and percentage of missing data at each visit will be reported.

The analyses will be performed on ITT population and a subject listing will be provided.

4.3.2.3.   Outcomes for Next Anticancer Therapy Following Study Treatment

The following data are collected in the eCRF for the next anticancer therapy following study treatment: Name of drug (and/or class), Start and Stop date, Progression date, Best response and Dose-limiting toxicities.

The lines of follow-up therapy are determined for each patient based on the reported start date(s) of follow-up therapies (excluding hormonal therapy) and the reported progression date(s) after the start of any follow-up therapy.

Hormonal therapy (PT: tamoxifen, tamoxifen citrate, toremifene, raloxifene, ospemifene, bazedoxifene, letrozole, anastrozole, exemestane) will not be considered for lines of follow-up therapy.

If there are one or more progression dates, all the reported follow-up therapies will be grouped into lines of therapies by comparing their reported start dates to the reported progression dates. The follow-up therapies started prior to the first progression date following the start of any follow-up therapy are grouped as the first line of follow-up therapy. The follow-up therapies started after the first progression date and prior to the second progression date are grouped as the second line of follow-up therapy, and so forth. If there is none of progression date reported, the reported follow-up therapies are grouped as the first line of follow-up anticancer therapy.

For each line of follow-up therapy, the start date of the line is the earliest start date of reported therapies in the line; the stop date of the line is the latest stop date of reported therapies in the line. All reported follow-up anticancer treatments will be summarized, including
- Any follow-up surgeries (yes or no)
- Any follow-up radiotherapy (yes or no)
- Number of lines of follow-up anticancer therapies
- Follow-up anticancer therapies

The follow-up anticancer therapies will be summarized according to Table 4 when applicable.

4.3.3.   Efficacy Sensitivity Analysis

For the primary PFS 18 and secondary PFS, a sensitivity analysis will be performed based on the Per Protocol population.

In addition, the following sensitivity analysis will be performed for PFS in ITT population by using different censoring rules.
- PFS Sensitivity analysis 1 (SA1): Ignore subsequent anti-cancer therapy
  - No evaluable baseline or post-baseline radiological tumor assessments, and no death or progression occurred within the two consecutive radiological tumor assessment intervals following the first dose (25-weeks time frame): censored at the first dose date
  - No progression or death: censored at the date of last evaluable radiological tumor assessment or the first dose date (whichever is later)
  - Progression or death after two or more consecutive missing radiological assessments: censored at the date of last evaluable radiological tumor assessment prior to the consecutive missing assessments or the first dose date (whichever is later)
  - Progression or death: event (whichever is earlier)
- PFS Sensitivity analysis 2 (SA2): Ignore missing tumor assessment

- o No evaluable baseline or post-baseline radiological tumor assessments, and no death or progression occurred within the two consecutive radiological tumor assessment intervals following the first dose (25-weeks time frame): censored at the first dose date

- o Start of subsequent anti-cancer therapy without a prior progression: censored at the date of last evaluable radiological tumor assessment on or prior to the start date of subsequent anti-cancer therapy, or the first dose date (whichever is later).

- o No progression or death and no subsequent anti-cancer therapy: censored at the date of last evaluable radiological tumor assessment or the first dose date (whichever is later)

- o Progression or death: event (whichever is earlier)

- • PFS Sensitivity analysis 3 (SA3): Include subsequent anti-cancer therapy as an event

  - o No evaluable baseline or post-baseline radiological tumor assessments, and no death or progression or subsequent anti-cancer therapy occurred within the two consecutive radiological tumor assessment intervals following the first dose (25-weeks time frame): censored at the first dose date

  - o No progression or death and no subsequent anti-cancer therapy: censored at the date of last evaluable radiological tumor assessment or the first dose date (whichever is later)

  - o Progression or death or start of subsequent anti-cancer therapy after two or more consecutive missing radiological assessments: censored at the date of last evaluable radiological tumor assessment prior to the consecutive missing assessments or the first dose date (whichever is later)

  - o Progression or death or start of subsequent anti-cancer therapy: event (whichever is earlier)

The PFS sensitivity censoring rules will impact the PFS event definition, which will consequently impact the primary PFS 18 evaluation. As such, the PFS 18 sensitivity analysis in the ITT population will also be performed accordingly.

The sensitivity analyses will not be performed at subgroup-levels.

4.3.4. Exploratory Efficacy Evaluations

The exploratory efficacy endpoints are PFS rate at 6 months (PFS6) and 12 months (PFS12), which are defined as the proportion of patients who have not progressed or died within 6 months and 12 months after initiation of treatment of niraparib in combination with bevacizumab treatment, respectively. Progression will be assessed by RECIST v1.1 criteria based on Investigator assessment. Additional landmark PFS analyses may be performed as deemed appropriate.

4.3.5. Biomarker Analysis

HRD will be evaluated retrospectively as a potential biomarker for response to niraparib combined with bevacizumab maintenance treatment using archival tumor sample. For patients

who do not have archival tissue, tissue from a fresh biopsy must be obtained prior to study treatment initiation.

4.4. Safety Analyses

Safety analyses will be conducted using the Safety population.

4.4.1. Niraparib Treatment Exposure

Extent of treatment will be summarized as follows:

- Number and percent of patients beginning 1, 2, 3, ..., 12, and >12 cycles.
- Number of cycles started summarized as a continuous variable.
- Overall treatment exposure (months), defined as the [last dose date - first dose date + 1] / 30.4375, will be summarize as a continuous variable.
- Actual treatment exposure (months), defined as the overall treatment exposure minus the duration of dose interruptions, will be summarized as a continuous variable.
- Time on study (months), defined as the [last contact date or date of death - first dose date + 1] / 30.4375, will be summarized as a continuous variable.

Treatment compliance will be summarized using study treatment data up to the last dose date by data cut-off date as follows:

- The total number of capsules consumed is the sum of the number of capsules dispensed minus the sum of the number of capsules returned by the patient during the study. The sum of the daily doses consumed (mg) is the total number of capsules consumed multiplied by the dosage (mg).
- Dose intensity (mg/day), defined as sum of the daily doses actually consumed divided by overall treatment exposure (converted to days), will be summarized as a continuous variable.
- Relative dose intensity (RDI, %), defined as dose intensity (mg/day) divided by intended dose intensity (mg/day), where intended dose intensity is the intended starting dose, will be summarized as a continuous variable.

Dose intensity, dose reductions and dose interruptions will be summarized by cycle:

- Number and percentage of patients with a dose reduction, as indicated on the dose modification eCRF, for any reason and due to an AE.
- Number and percentage of patients with a dose interruption, as indicated on the dose modification eCRF, for any reason and due to an AE.

Dosing information and capsule counts for each patient will be presented in a data listing.

4.4.2. Bevacizumab Treatment Exposure

Treatment exposure will be summarized as follows:

- Number and percent of patients beginning 1, 2, 3, ..., 12, and >12 cycles.

- Number of cycles started summarized as a continuous variable.
- Overall treatment exposure (months), defined as the [last dose date - first dose date + 21] / 30.4375, will be summarize as a continuous variable.

Treatment compliance will be summarized using study treatment data up to the last dose date by data cut-off date as follows:

- Cumulative dose (mg) is calculated as sum of all actual dose infused.
- Dose intensity (mg/kg/cycle) is calculated as cumulative dose divided by weight and duration of treatment ([last dose date - first dose date + 21]/21).
- Relative dose intensity (RDI, %) is calculated as dose intensity (mg/kg/cycle) divided by intended dose intensity (mg/kg/cycle) multiplied by 100, where the intended dose intensity is 15mg/kg/cycle.
- Dose intensity, infusions missing, and infusion interruptions will be summarized by cycle

Infusion information for each patient will be presented in a data listing.

4.4.3. Adverse Events

4.4.3.1. Overview

All AEs will be classified using MedDRA v20.0 or later. The severity of the toxicities will be graded according to the NCI CTCAE v4.03. Any AEs leading to death or discontinuation of study treatment, events classified as NCI CTCAE v4.03 Grade 3 or higher, study treatment-related events, and SAEs will be presented.

Treatment emergent AEs (TEAEs) will be defined as:

- Any new AE (one that was not seen prior to the start of treatment) that occurs for the first time after at least 1 dose of study treatment has been administered; or,

- A preexisting condition (one that was seen prior to the start of treatment) that worsens in severity or is deemed by the investigator to be related to study drug after at least 1 dose of study treatment has been administered.

- Note: If the start date is missing for an AE and the actual start date cannot be determined from a partial date, the AE will be considered treatment-emergent.

- Note: AEs with a start date after 90 days after the last dose of study treatment will not be considered treatment emergent.

AEs and SAEs will be collected and recorded in the eCRF for each patient from the day of signed main informed consent until 90 days after the last dose of study treatment or until the patient begins participation in a new clinical trial or initiates a new chemotherapy regimen, whichever occurs first. Patients will be followed until study closeout for study-drug related SAEs.

MDS/AML and secondary cancers (new malignancies other than MDS or AML) must be reported until death or loss to follow-up. Pneumonitis must be reported for up to 90 days after the last dose of study treatment and pregnancy must be reported for up to 180 days after the last dose of study treatment.

Any AEs recorded in the database that occur from the time of informed consent to first dose will be listed only and not included in safety analyses. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

Related TEAEs are defined as TEAEs related to treatment as judged by the Investigator. Any AEs for which the relationship to study drug is missing will be considered as related to study treatment. Unless otherwise specified, related analysis will be based on related to niraparib, bevacizumab, and any study treatment, respectively.

The number and percentage of patients reporting a TEAE will be summarized by system organ class (SOC), preferred term (PT), toxicity grade, and relationship to study drug.

The toxicity grade of AEs as assessed by the investigator will be graded using NCI CTCAE v4.03. Within the same MedDRA PT, only the most severe AE for each patient will be counted in tabulations by severity. Within a MedDRA SOC, patients with more than 1 MedDRA PT will be counted only once for the most severe AE reported.

The relationship of each AE to the study drug will be summarized as assessed by the Investigator. All AEs for which the relationship to study drug is missing will be considered as related. Within the same MedDRA PT, only the AE with the highest ranked relationship to treatment for each patient will be counted in tabulations by relationship to treatment. Within a MedDRA SOC, patients with more than 1 MedDRA PT will be counted only once for the AE that is most related to treatment. The imputation for a missing relationship will take place prior to determining the most related AE within a SOC or PT for a given patient.

The following lists the AE tables to be displayed for all safety population. Summaries designated with an asterisk ("*") were produced for the safety population for the subgroup of age (< 65 years vs ≥ 65 years).

- Overview of TEAEs*
- TEAE by SOC and PT*
- TEAE by PT (sorted by frequency)
- Related TEAE by SOC and PT
- Related TEAE by PT (sorted by frequency)
- Treatment-emergent SAEs by SOC and PT*
- Related treatment-emergent SAEs by SOC and PT
- Grade ≥3 TEAEs by SOC and PT*
- Related Grade ≥3 TEAEs by SOC and PT
- Grade ≥3 treatment-emergent SAEs by SOC and PT
- Related Grade ≥3 treatment-emergent SAEs by SOC and PT
- Grade ≥3 TEAE by PT (sorted by frequency)
- Related Grade ≥3 TEAE by PT (sorted by frequency)
- SAE by PT (sorted by frequency)

- Related SAE by PT (sorted by frequency)
- Grade ≥3 treatment-emergent SAEs by PT (sorted by frequency)
- Related Grade ≥3 treatment-emergent SAEs by PT (sorted by frequency)
- TEAE by SOC, PT, and maximum grade
- Related TEAE by SOC, PT, and maximum grade
- Grade ≥3 TEAE by SOC, PT, and maximum grade
- Grade ≥3 Related TEAE by SOC, PT, and maximum grade
- TEAEs leading to death by SOC and PT
- Related TEAEs leading to death by SOC and PT
- TEAEs leading to study drug dose interruption by SOC and PT
- TEAEs leading to study drug dose reduction by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT*
- TEAEs leading to study drug infusion delay by SOC and PT
- Adverse events of special interest (AESI), by the grouped event and PT within each group
    - All AESI
    - Grade ≥3 AESI
    - Serious AESI
    - Grade ≥3 Serious AESI
    - AESI leading to study drug dose interruption
    - AESI leading to study drug dose reduction
    - AESI leading to study drug discontinuation
    - AESI leading to study drug infusion delay

- Treatment-emergent Adverse events of medical interest (AEMI), by the grouped event and PT within each group
    - All TEAE*
    - Grade ≥3 TEAE*
    - Treatment-emergent SAEs
    - Grade ≥3 Treatment-emergent SAEs
    - TEAEs leading to study drug dose interruption
    - TEAEs leading to study drug dose reduction
    - TEAEs leading to study drug discontinuation *

      ○ TEAEs leading to study drug infusion delay

- Non-serious TEAEs observed in at least 5% of patients by SOC and PT
- Summary of Treatment Related Treatment-Emergent non-Serious Adverse Events by MedDRA Preferred Term in Descending Frequency Order
- Summary of Niraparib Related Treatment-Emergent non-Serious Adverse Events by MedDRA Preferred Term in Descending Frequency Order
- Summary of Niraparib Related Treatment-Emergent non-Serious Adverse Events by MedDRA Preferred Term in Descending Frequency Order

For COVID-19 positive subjects who were diagnosed with probable, suspected or confirmed COVID-19, the following AE summary will be provided.

- COVID-19 related TEAE by SOC and PT
- COVID-19 related Grade ≥3 TEAE by SOC and PT
- COVID-19 related treatment-emergent SAEs by SOC and PT
- COVID-19 related Grade ≥3 treatment-emergent SAEs by SOC and PT

The COVID-19 related AE SOC and PT list is provided in a separate document.

Tables structured as listings will be provided for the following:

- AEs
- SAEs
- TEAE leading to Death
- TEAEs leading to study drug dose interruption
- TEAEs leading to study drug dose reduction
- TEAEs leading to study drug discontinuation
- TEAEs leading to study drug infusion delay
- AESI
- Treatment-emergent Adverse events of medical interest
- Listing of COVID-19 Assessments and Symptom Assessments for COVID-19 Positive Subjects

Adverse event summaries will be ordered in terms of decreasing frequency for SOC (alphabetically for SOCs with the same number of AEs reported) and decreasing frequency for PT within SOC (alphabetically for PTs with the same number of AEs reported within a SOC).

4.4.3.2.   Adverse Events of Special Interest

The AESIs for this study are myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), secondary cancers (new malignancies other than MDS/AML), pneumonitis, and embryo-fetal toxicity. Table 5 outlines the AESI with the criteria of mapping MedDRA PTs for each AESI using Standardized MedDRA Queries (SMQs), High Level Terms (HLTs), and/or PTs.

Table 5:   Adverse Events of Special Interest

Group Term	MedDRA V18.1 Criteria for Selection of Preferred Terms[1]
AESI (MDS/AML events)	MedDRA PTs associated with MDS/AML
AESI (new malignancies other than MDS/AML)	Malignant tumor SMQ (other than MDS/AML)
AESI (pneumonitis)	Lower respiratory tract inflammatory and immunologic conditions (HLT)
AESI (embryo-fetal toxicity)	Pregnancy and neonatal topics SMQ

Abbreviations: AESI = adverse event of special interest; AML = acute myelogenous leukemia; HLT = high-level term; MDS = myelodysplastic syndrome; MedDRA = medical dictionary for regulatory activities; PT = preferred term; SMQ = Standardized MedDRA Query.

4.4.3.3.   Adverse Events of Medical interest

AEs of Medical interest (AEMI) such as myelosuppression and hypertension will be summarized in the similar manner as the AESIs. Table 6 outlines all the grouped events with the criteria of mapping MedDRA PTs for each group using Standardized MedDRA Queries (SMQs), High Level Terms (HLTs), and/or PTs.

Table 6:   Adverse Events of Medical interest

Group Term	MedDRA Criteria for Selection of Preferred Terms[1]
Thrombocytopenia events	Haematopoietic thrombocytopenia SMQ (Broad)
Anemia events	Haematopoietic erythropenia SMQ (Broad)
Leukopenia events	Haematopoietic leukopenia SMQ (Broad)
Neutropenia events	Selected PTs related to neutropenia in the Haematopoietic leukopenia SMQ (Broad)
Pancytopenia events	Haematopoietic cytopenias SMQ (Broad)
Hypertension events	Hypertension SMQ

Abbreviations: AESI = adverse event of special interest; AML = acute myelogenous leukemia; HLT = high-level term; MDS = myelodysplastic syndrome; MedDRA = medical dictionary for regulatory activities; PT = preferred term; SMQ = Standardized MedDRA Query.

The MedDRA PTs for AESI and adverse Events of Medical interest list are provided in a separate document.

4.4.4. Laboratory Data

Laboratory assessments will be performed locally at each center's laboratory by means of their established methods. All laboratory values will be converted to SI units and classified as normal, low, or high based on normal ranges supplied by the local laboratories.

Hematologic and chemistry laboratory results will be graded according to the cut points defined in the NCI CTCAE v4.03 severity grade. Laboratory results will be summarized by maximum CTCAE grade as available. Abnormal laboratory findings will be summarized by CTCAE grade 1-4 and grade 3-4, respectively and sorted by frequency of grade 3-4.

Continuous results will be analyzed using change from baseline and shift values. Change from baseline will be summarized and analyzed according to the largest increase, decrease, and at EOT, irrespective of scheduled or unscheduled visit. Graphical line mean changes over time may be provided, but due to the varying visits, no repeated measures analysis will be performed.

Shift from baseline to the smallest value, the largest value, and the EOT value, categorized as low, normal, or high relative to the normal range, will be reported using number and percentage of patients. Shift from baseline CTCAE grade to the post-baseline maximum CTCAE grade will also be reported.

A listing of potential Hy's Law cases (patients with AST or ALT ≥ 3 ×upper limit of normal [ULN] in combination with bilirubin ≥ 2 ×ULN) will be also presented.
Additionally, a Hy's Law (DILI) plot will be produced which plots peak ALT and peak total bilirubin in 1 panel and peak AST and peak total bilirubin in a second panel.

A by-patient listing of all laboratory data will be provided, with laboratory reference ranges and abnormal values highlighted, CTCAE grade if applicable, and including center, patient identifier, and visit.

4.4.5. Vital Signs and Physical Examination

Summaries of vital signs parameters (systolic and diastolic blood pressures, pulse rate, and temperature) and weight will be presented by visit. Summary statistics will be produced for both observed and change from baseline values, for each parameter.

Change from baseline will be summarized and analyzed according to the largest increase, decrease, and at the EOT, irrespective of scheduled or unscheduled visit. Graphical line mean changes over time may be provided, but due to the varying visits no repeated measures analysis will be performed.

A summary table of the number and percent of patients categorized as low or high at any time

on study after baseline according to the below criteria will be presented.

- SBP (mm Hg):
    - Low: <90 and decrease from baseline ≥ 20
    - High: >160 and increase from baseline ≥ 20
- DBP (mm Hg):

- Low: <50 and decrease from baseline ≥10

- High: >100 and increase from baseline ≥10

Vital sign measurements will be presented for each patient in a data listing.

The number and percentage of patients experiencing at least 1 abnormal result at the baseline physical examination will be summarized by body system. Physical examination findings will also be presented for each patient in a data listing.

ECOG performance status will be reported in a data listing.

Screening ECG data will be summarized for each ECG parameter and will be provided in a data listing for each patient.

4.4.6.   Concomitant Medications

All medications will be coded using the September 2017 or later version of the WHO Drug Dictionary (WHODD).

Medication start and stop dates will be compared to the date of first dose of study drug to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the treatment withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study drug will be classified as Prior only. If a medication starts before the date of first dose of study drug and stops on or after the date of first dose of study drug, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study drug. Concomitant medication will be summarized by ATC level 3 and PT in frequency tables by treatment. Patients with more than 1 medication in a given ATC level and PT will be counted only once in that category.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study drug. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study drug. If there is clear evidence to suggest that the medication started prior to the first dose of study drug, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study drug. If there is clear evidence to suggest that the medication stopped prior to the first dose of study drug, the medication will be assumed to be Prior only. The following lists the concomitant medication tables to be displayed:

- Number and percentage with at least 1 prior medication by ATC level 3 and PT

- Number and percentage with at least 1 concomitant medication by ATC level 3 and PT

- Number and percentage with at least 1 prior and concomitant medication by ATC level 3 and PT

The use of concomitant medications will be included in a by-patient data listing.

5. CHANGES TO PLANNED ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and those presented in this SAP.

If any modifications in the experimental design, dosages, parameters, patient selection, or any other sections of the protocol are indicated or required, the Investigator will consult with the Sponsor before such changes are instituted. Modifications will be accomplished through formal amendments to this protocol by the Sponsor and approval from the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

6. REFERENCES

Beaumont J, Yount S, Lalla D, et al. Validation of the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) Symptom Index (FOSI) in a Phase II Clinical Trial of Pertuzumab in Patients with Advanced Ovarian Cancer. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings (Post-Meeting Edition). 2007;25(18S):16021.

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Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009;45(2):228-47.

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7. APPENDIX

7.1. Sample Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

7.2. Scoring Algorithm for the FACT/NCCN Ovarian Symptom Index (FOSI)

FACT/NCCN Ovarian Symptom Index (FOSI)

Scoring Guidelines (Version 4)

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

8. STATISTICAL OUTPUT SHELLS

The list of statistical output and corresponding table/figure/listing shells are provided in a separate document.

9.   REVISION HISTORY

N/A