Protocol

Study ID: 213357-Cohort-C

Study Official Title: A Phase 1B/2 Multicohort Umbrella Study to Evaluate the Safety and Efficacy of Novel Treatments and/or Combinations of Treatments in Participants with Ovarian Cancer (OPAL) (PR-3000-02-005/213357)

Cohort C: Open-label Phase 2, Randomized, Controlled Multicenter Study Comparing Niraparib Versus Platinum-Taxane Doublet Chemotherapy as Neoadjuvant Treatment in Participants with Homologous Recombination-deficient Stage III/IV Ovarian Cancer

NCT ID: NCT06964165

Date of Document: 31 Oct 2023

Note: 213357 is a master protocol, registered under the identifier NCT03574779. It includes independent sub-studies, Cohort A (NCT05751629) and Cohort C (NCT06964165), each separately registered on ClinicalTrials.Gov. This is a cohort C-specific protocol. Please refer to the Master Protocol (NCT03574779) for general protocol elements.

SUPPLEMENT C
3000-02-005
COHORT C: OPEN-LABEL PHASE 2, RANDOMIZED, CONTROLLED MULTICENTER STUDY COMPARING NIRAPARIB VERSUS PLATINUM-TAXANE DOUBLET CHEMOTHERAPY AS NEOADJUVANT TREATMENT IN PARTICIPANTS WITH HOMOLOGOUS RECOMBINATION-DEFICIENT STAGE III/IV OVARIAN CANCER

Sponsor:

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Clinical Research Organization:	Not applicable
IND No.:	100,996
EudraCT No.:	2021-005392-39
EU CT Number	2023-505097-16-00
Development Phase:	2
Date of Original (Version 1.0) Master Protocol:	20 March 2018
Date of Master Protocol Amendment 1 (Version 2.0):	15 October 2021
Date of Master Protocol Amendment 2 (Version 3.0):	26 October 2023
Version of Protocol Supplement C:	2.0
Date of Original (Version 1.0) Protocol Supplement C:	15 October 2021
Date of Protocol Supplement C Amendment 1 (Version 2.0):	31 Oct 2023

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

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This cohort-specific protocol supplement was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

Jimmy Belotte, MD, PhD Medical Director, GSK	Date

INVESTIGATOR'S AGREEMENT

I have read this cohort-specific protocol supplement, including all appendices. By signing this supplement, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol (comprising the master protocol and this cohort-specific supplement), the current International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki (2013), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this cohort-specific protocol supplement and will receive all necessary instructions for performing the study according to the study protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1 (Version 2.0)	31 Oct 2023
Original Protocol (Version 1.0)	15 October 2021

Amendment 1 (31 Oct 2023)

This amendment is considered substantial based on the criteria defined in European Union (EU) Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because the changes significantly impact the scientific value of the study and safety of the participants.

Overall Rationale for the Current Amendment:

Amendment 1 is a global amendment resulting from changes in the Statstical Analysis Plan (SAP) and analysis populations, as well as clarification for study conduct.

A general description and brief rationale for the changes are provided in the table below. The synopsis was updated to align with the changes in the protocol body.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Headers, title page, abbreviations, Protocol Amendment Summary of Changes (new), List of Abbreivations, Procedures in Case of Emergency, References, and throughout	Headers and title page were updated with new document number and amendment information; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment; editorial revisions for consistency with Sponsor's ways of working, minor corrections and formatting adjustments, and to add clarification and/or remove discrepancies.	Editorial changes to align with the Sponsor's standard protocol template, style guide, and ways of working and for accuracy, clarity, conformity, flow, and typographical error correction.

Section # and title	Description of change	Brief rationale
Section 6.3 Exploratory Objectives Section 7.2 Number of Participants Section 11.2 Secondary Efficacy Endpoints Section 11.4 Exploratory Endpoints Section 13.2 Planned Analyses Section 13.2.1 Analysis Populations Section 13.2.2.1 Primary Efficacy Analysis Section 13.2.2.2. Secondary Efficacy Analysis Section 13.2.2.3 Exploratory Efficacy Analysis Section 13.2.5 Interim Analysis	Changes in statistical endpoints and analysis text include the following: • Updated the primary analysis population to the Intent-to-Treat (ITT) Population • CCI [redacted] • Clarification included regarding timing and minimum maturity for time-to-event endpoints of the planned analyses • Progression-free survival (PFS) rates removed as secondary endpoints and will instead be assessed as part of the PFS analysis • Analysis Populations revised to remove additional analysis populations	Clarifications and corrections made to planned statistical analyses. Additional analysis populations removed from protocol but included in the SAP to prevent duplication. Additional exploratory efficacy endpoints were added to further evaluate clinical efficacy.
Section 7.4.1.1 Niraparib, (Niraparib Dose Interrupation and Modification) Table 3 Nirapairb Dose Modifications for Nonhematological Toxicity Table 4 Niraparib Dose Modifications for Hematologial Toxicity	Niraparib interruption updated to indicate interruption allowed for up to 28 days	To align with Global Data Sheet (GDS)/Investigator's Brochure (IB)
Section 10.5.1 Niraparib	Study drug administration updated to include guidance for niraparib starting dose in the maintenance period for participants who received niraparib in the neoadjuvant period and experienced dose reductions	To clarify and provide guidance on maintenance period starting dose for participants who experienced niraparib dose reductions due to AEs in the neodjuvant period to ensure participant safety.
Table 5 (Schedule of Events) Section 7.6.7 Safety Assessments	Baseline electrocardiogram (ECG) monitoring added for all participants and as needed throughout the study based on patient cardiovascular risk profile. Footnote included in Table 5 for clarification.	To align with safety monitoring for participants receiving niraparib

Section # and title	Description of change	Brief rationale
Section 8.1 Inclusion Criteria	Update inclusion criterion C7 to permit enrollment of participants with g*BRCA* test	To allow enrollment of patients with permitted g*BRCA* test without waiting for results of the central test, as high concordance is expected between Sponsor's permitted test and central test results.
Section 8.3.1 Discontinuation from Treatment Section 8.3.2 Discontinuation from Study	Additional text surrounding data collection including overall survival (OS) data collection in long-term follow-up after withdrawal of consent or lost-to-follow up	Clarification for study conduct and collection of OS data for analysis
Section 11.1 Primary Efficacy Endpoint Section 11.3 Patient-reported Outcome Endpoints Section 13.2.4 Safety Analyses	• Updated primary endpoint wording to unconfirmed ORR for clarification • Correction to exploratory patient-reported outcome (PRO) endpoint wording to align with data collection in Table 5 • Clarification to define population for Safety Analyses	Clarification statistical endpoints, data collection, and analyses
Section 7.1 Overall Study Design Table 5 Schedule of Events	Clarification surrounding the Safety Follow-up Visit. Removed text regarding EOT scan for those with PD in text and footnotes, which was included in error.	Clarification for study conduct. Safety Follow-up visits required for all participants following end-of-treatment.
Title Page Section 5.5 Benefit/Risk Assessment (new) Section 7.1.6 End of study definition	EU CT number added Benefit-risk text added End of study definition included along with follow-up time	To align with the Sponsor's protocol template and components aligned with EU CTR
Figure 2 (Study Schema) Section 7.1.2 Neoadjuvant Treatment Period Section 9.4 Randomization and Blinding Section 13.1 Sample Size Determination Section 13.2.2.2 Secondary Efficacy Analysis	Clarified stratification for *BRCA* mutational status (*BRCAmut* vs *BRCAwt*/unknown) Added text in sample size determination section indicating additional participants may be randomized for drop-out	Clarification for study conduct

Section # and title	Description of change	Brief rationale
Section 7.1.2 Neoadjuvant Treatment Period Section 7.1.3 IDS Period	Updates, including new figure (Figure 1) to better describe the process for going into IDS after pre-IDS scan	Clarification in study conduct
Section 7.1.5 Maintenance Treatment Period Table 5 Schedule of Events (footnote) Section 7.6.3.1 RECIST v1.1	Extended visit window for imaging assessments at 6 months to ± 14 days	Adjusted visit window for maintenance assessment for visits after 1 year
Table 5 Schedule of Events Section 7.4.1.1 Niraparib (Hypertension, Including Hypertensive Crisis)	Clarifications added in table foonote regarding regarding blood pressure and heart rate monitoring and timing of assessments and data collection.	Clarification for study conduct for participant safety monitoring
Table 5 Schedule of Events Section 7.6.6 Patient-reported Outcome Questionnaires	Updated text (and footnote added in Table 5) to indicate ePROs should be done before any procedure at all visits	Clarification for study conduct to align with intended procedures
Table 5 Schedule of Events Section 7.6.7 Safety Assessments	Updated text to indicate adverse event (AE) collection/reporting should begin at the time of signing Prescreening Informed Consent Form (ICF)	Clarification in study conduct for AE reporting
Table 5 Schedule of Events (footnote) Section 7.6.10 Tumor Tissue and Blood Sampling	Clarification added regarding number of PK samples collected predose and window for taking samples	Clarification in study conduct to align with procedures outlined in the Study Reference Manual
Table 5 Schedule of Events (footnote)	Clarification added surrounding complete blood count (CBC) and timing of assessements.	Clarification for study conduct and safety monitoring in the niraparib arm.
Section 8.2 Exclusion Criteria	Minor updates in wording to exclusion criterion #C9 for clarification	Clarification in study conduct
Section 9.1, Table 6 Study Drugs	Added row to clarify which study treatments are investigational medicinal (IMP) products vs non-IMP/auxiliary medicinal products.	Clarification per regulatory feedback received during first submission, and for clairty and completness

Section # and title	Description of change	Brief rationale
Table 5 Schedule of Events (footnote) Section 9.2.2 Contraception	Contraception and pregnancy testing requirements clarified	Clarification for study conduct
Section 7.6.2 Treatment Cycles Section 7.6 Study Conduct, Table 5 Schedule of Events	• Visit windows added to Schedule of Events (C1D8, C1D15, C1D1, C2D1, C3D1) and language surrounding Long-term Follow-up Visits • Symptom-directed physical examination included for C1D8 and C1D15 • Clarifications added in footnotes regarding AE and concomitant medications data collection	Clarification and consistency within the protocol, with intended procedures, with Informed Consent Form (ICF) wording and local standard of care practice
Section 10.2 Study Drug Packaging and Labeling Section 10.7 Study Drug Handling and Disposal	Updated to include location of detailed information for additional study interventions.	Clarity and completeness and clarification for details related to carboplatin-paclitaxel, and bevacizumab, as well as description of niraparib study drug.
Section 13.2.4.1 Pharmacokinetic and Pharmacodynamic Analyses	Removed statement regarding responsibility for analysis.	Clarification and alignment with anlaysis process.
Appendix B, Table 7 Liver Chemistry Stopping Criteria and Required Follow-up Assessments	Updated langauge to reference liver event eCRF Updated timing for obtaining blood PK sample	Clarification in study conduct and sample collection surrounding liver event assessment

PROCEDURES IN CASE OF EMERGENCY

Procedures in case of emergency are outlined in the Supplement C Study Reference Manual.

2. SYNOPSIS

Name of Sponsor/Company: TESARO Inc., a GSK company	
Name of Investigational Product: Niraparib	
Name of Active Ingredient: Niraparib	
Title of Study: Phase 1B/2 Multicohort Umbrella Study to Evaluate the Safety and Efficacy of Novel Treatments and/or Combinations of Treatments in Participants with Ovarian Cancer **Cohort C:** Open-label Phase 2, Randomized, Controlled Multicenter Study Comparing Niraparib Versus Platinum-Taxane Doublet Chemotherapy as Neoadjuvant Treatment in Participants with Homologous Recombination-Deficient Stage III/IV Ovarian Cancer	
Study center(s): Multicenter global	
Principal Investigator: To be determined **Investigators:** Multicenter (a list is provided in the Study Reference Manual)	
Studied period (years): Estimated date first participant enrolled: Q4 2021 Estimated date last participant completed: Q4 2025	**Phase of development:** 2

Objectives:

Primary:

- To evaluate the efficacy of neoadjuvant niraparib compared with neoadjuvant platinum-taxane doublet chemotherapy after 1 induction cycle of carboplatin-paclitaxel per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in participants with confirmed homologous recombination-deficient (HRd) Stage III to IV ovarian cancer (OC)

Secondary:

- To evaluate clinical benefit by Gynecological Cancer InterGroup (GCIG) cancer antigen 125 (CA-125) response criteria
- To evaluate clinical benefit as measured by progression-free survival (PFS) per RECIST v1.1 by investigator assessment
- To evaluate participants' reported overall tolerability toward treatment, overall health status, OC-specific health-related quality of life (HRQoL) and symptoms, and work productivity
- To evaluate clinical benefit as measured by overall survival (OS)
- To evaluate clinical benefit as measured by time to first subsequent treatment (TFST)
- To evaluate the safety and tolerability of neoadjuvant niraparib and neoadjuvant platinum-taxane doublet chemotherapy

CCI [redacted]

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Methodology:

This is a global, multicenter, randomized, open-label, Phase 2 cohort in participants with newly diagnosed, Stage III or IV, high-grade non-mucinous epithelial ovarian, fallopian tube, or peritoneal cancer (collectively referred to as "ovarian cancer" or OC) who are eligible for neoadjuvant platinum-taxane doublet chemotherapy followed by interval debulking surgery (IDS). This study will enroll participants with HRd OC as determined by the central tumor homologous recombination deficiency (HRD) testing using a fully validated assay. All prescreened participants would have received, prior to enrollment, 1 cycle of standard of care (SOC) chemotherapy (i.e., carboplatin-paclitaxel) to allow sufficient time for receipt and review of the biomarker test results.

After confirmation that the tumor is HRd, participants will be randomized 1:1 to three 21-day cycles of platinum-taxane doublet chemotherapy (Arm 1; carboplatin-paclitaxel, unless not tolerated by the participant) or neoadjuvant niraparib (Arm 2). After 3 cycles of treatment, the participants will undergo IDS.

After IDS, all participants will receive up to three 21-day cycles of platinum-taxane doublet chemotherapy (Cycles 4, 5, and 6), with the third cycle (Cycle 6) being optional (any site choosing to give the third cycle must offer the third cycle to all eligible participants treated at that site regardless of the arm the participant was enrolled onto). The Investigator may choose to administer bevacizumab or bevacizumab biosimilar in addition to platinum-taxane doublet chemotherapy as SOC therapy for a participant deemed high-risk. Any site that chooses to provide optional bevacizumab or bevacizumab biosimilar as SOC must offer it to all eligible high-risk participants treated at that site, regardless of enrollment arm.

Adjuvant chemotherapy is followed by niraparib maintenance treatment for up to 36 months or until adverse event (AE), progression of disease (PD) per RECIST v1.1, risk to participant or participant's severe noncompliance with protocol as judged by the Investigator or Sponsor, participant's request, pregnancy, or end of study. Participants that are administered bevacizumab or bevacizumab biosimilar with chemotherapy after IDS may continue to receive it in addition to niraparib during the maintenance treatment period for up to 22 cycles (including adjuvant chemotherapy period). Participants who discontinue study treatment prior to an investigator assessment of PD per RECIST v1.1 will continue radiographic imaging until PD per RECIST v1.1, start of alternate anticancer therapy, participant discontinuation of the study, withdrawal of consent to study procedures, becoming lost to follow-up, death, or end of the study.

Participants will be followed up for safety for 30 days (±7 days) after completion of study treatment. After the Safety Follow-up Visit, all participants will enter the posttreatment follow-up period of telephone assessment for survival status, assessment of subsequent anticancer therapy, and the occurrence of any adverse event of special interest (AESI) every 90 days (±14 days) until participant discontinuation of the study, withdrawal of consent, death, or end of study. Radiographic imaging will continue as scheduled during the posttreatment follow-up period for all participants without PD per RECIST v1.1 until PD per RECIST v1.1, start of alternate anticancer therapy, participant discontinuation of the study, withdrawal of consent to study procedures, becoming lost to follow-up, death, or end of the study.

Primary efficacy endpoint is pre-IDS unconfirmed ORR; defined as the percentage of participants with unconfirmed complete or partial response) per RECIST v1.1 by investigator assessment.

Secondary endpoints include CA-125 progression by GCIG CA-125 response criteria; PFS; patient-reported outcomes to evaluate overall tolerability to treatment, overall health status, OC-specific HRQoL and symptoms, and work productivity; OS; TFST; and safety and tolerability. Exploratory endpoints include surgical and postsurgical outcomes, as well as pre-IDS DCR, pre-maintenance unconfirmed ORR, and pre-maintenance DCR. CCI [redacted]

All participants must provide 2 formalin-fixed paraffin-embedded tissue blocks (or slides if blocks are not available) with sufficient tumor content (as confirmed by the sponsor's designated central and/or testing laboratory) for central HRD testing at Prescreening and exploratory biomarker testing at Prescreening or Screening. If sufficient tumor tissue is provided at Prescreening, participants do not need to provide additional tissue at Screening. Participants will be required to provide sufficient tumor sample collected during IDS. Blood samples will be collected for exploratory biomarker testing, including evaluation of circulating plasma biomarkers CCI [redacted]) and CCI [redacted]. Blood samples will be collected at Prescreening, Cycle 1 Day 1, pre-IDS, Cycle 4 Day 1, Maintenance Cycle 1 Day 1 and every 3 months thereafter, the End-of-Treatment Visit, and the Safety Follow-up Visit.

The Cohort C study schema is provided below.

CCI [redacted]

Note: Duration of study periods are as follows:
- Prescreening: 5 weeks
- Screening: 1 week
- Neoadjuvant treatment: up to 12 weeks
- IDS: up to 6 weeks
- Adjuvant platinum-taxane chemotherapy and optional bevacizumab or bevacizumab biosimilar: 6 to 9 weeks*
- Niraparib maintenance: up to 36 months. Optional bevacizumab or bevacizumab biosimilar may be administered for up to 22 cycles (including adjuvant chemotherapy period).

*Note: Cycle 6 is optional. If a site chooses to administer cycle 6 (C6) of adjuvant chemotherapy, all participants treated at this study site must be offered C6 of adjuvant chemotherapy, regardless of treatment received during the neoadjuvant treatment period. Any site that chooses to provide optional bevacizumab or bevacizumab biosimilar as SOC to eligible high-risk participants must offer it to all eligible high-risk participants treated at that site, regardless of enrollment arm.

Stratification: *BRCAmut* (deleterious or suspected deleterious *BRCA1* or *BRCA2* mutation) vs *BRCA*wt/unknown (no deleterious or suspected deleterious *BRCA1* or *BRCA2* mutation; including unknown)

Abbreviations: *BRCA*=breast cancer gene; *BRCA*mut=*BRCA* mutant; *BRCA*wt=*BRCA* wildtype; C=cycle; carbo=carboplatin; chemo=chemotherapy; CR=complete response; Cx=cycle number; endpt=endpoint; EU=European Union; HR=homologous recombination; HRd=homologous recombination-deficient; ICF=informed consent form; IDS=interval debulking surgery; mPFS=median progression-free survival; NVRD=no visual residual disease; ORR=overall response rate; OS=overall survival; pathCR=pathological complete response; PD=pharmacodynamics; PFS=progression-free survival; PK=pharmacokinetics; PRO=patient-reported outcome; QD=once daily; R=randomization; SOC=standard of care; TFST=time to first subsequent treatment; xxm=xx months

CCI [redacted]

Diagnosis and main criteria for inclusion:

The overall list of eligibility criteria for entry into this study is provided in the master protocol. All eligibility criteria for this cohort (Cohort C) are included in this cohort-specific supplement. Participants must meet all criteria to be eligible for enrollment in this cohort.

Key inclusion criteria are as follows:

Key inclusion criteria from the master protocol

- Participant must be female ≥18 years of age, able to understand the study procedures, and agree to participate in the study by providing written informed consent.
- Participant must have measurable disease according to RECIST v1.1.

Key inclusion criteria specific to this cohort (Cohort C)

- Participant has newly diagnosed Stage III or IV ovarian, fallopian tube, or primary peritoneal cancer according to the International Federation of Gynecology and Obstetrics staging criteria.
- Participants must provide sufficient tumor tissue at Prescreening and agree to undergo a central HRD tumor testing using a fully validated assay. The participants must be HRd as per central HRD tumor testing result for eligibility.
    - Participants with a documented germline breast cancer gene (*BRCA*)1/2 deleterious or suspected deleterious mutations by Sponsor's permitted test (e.g., CCI [redacted] may be allowed to enroll prior to receiving the central test results, provided all inclusion criteria are met. However, tumor sample submitted by these participants will still be required for central HRD confirmation. The list of Sponsor's permitted tests will be provided by the Sponsor.
    - All participants must agree to provide tumor tissue collected from IDS.
    - Participant must provide 2 formalin-fixed paraffin-embedded tissue blocks (or slides if blocks are not available) with sufficient tumor content (as confirmed by the Sponsor's designated central and/or testing laboratory) for central HRD testing at Prescreening and for exploratory biomarker testing at Prescreening or Screening. If sufficient tumor tissue is provided at Prescreening, participants do not need to provide additional tissue at Screening.
- Participant must have completed 1 run-in cycle of carboplatin-paclitaxel and not experienced disease progression after this treatment. Completion is defined as receiving ≥50% of the prescribed dose of therapy within 5 weeks.
- Participant must not have known contraindication or uncontrolled hypersensitivity to carboplatin and paclitaxel and their excipients and no known pre-existing conditions that would preclude treatment with these agents.

- Participant must not have known contraindication or uncontrolled hypersensitivity to niraparib and its excipients.
- Participant must not have symptomatic ascites or pleural effusions as defined by the following criterion: presence of fluid in the abdominal or pleural cavities requiring removal within 1 week prior to signing the informed consent.
- Participant must agree to complete patient-reported outcome (PRO) and work productivity questionnaires throughout the study.

Main criteria for exclusion:

Key exclusion criteria are as follows:

Key exclusion criteria from the master protocol (none)

Key exclusion criteria specific to this cohort (Cohort C)

- Participant has low-grade or Grade 1 epithelial OC or mucinous, germ cell, transitional cell, carcinosarcoma, or undifferentiated tumor.
- Participant has contraindications to surgery.
- Participant has a bowel obstruction by clinical symptoms or computed tomography scan, subocclusive mesenteric disease, abdominal or gastrointestinal fistula, gastrointestinal perforation, or intra-abdominal abscess.
- Participant has any known history or current diagnosis of myelodysplastic syndrome or acute myeloid leukemia.
- Participant is at increased bleeding risk due to concurrent conditions (e.g., major injuries or major surgery within the past 28 days prior to the start of study treatment and/or history of hemorrhagic stroke, transient ischemic attack, subarachnoid hemorrhage, or clinically significant hemorrhage within the past 3 months).
- Participant received prior treatment for high-grade non-mucinous epithelial ovarian, fallopian tube, or peritoneal cancer (e.g., prior surgery, immunotherapy, anticancer therapy [with the exception of 1 run-in cycle of carboplatin-paclitaxel], or radiation therapy).
- Participant is unable to swallow orally administered medication or has a gastrointestinal disorder likely to interfere with absorption of the study medication.
- Participant received whole blood transfusions in the 2 weeks prior to entry to the study (packed red blood cells and platelet transfusions are acceptable outside of 2 weeks prior to treatment).

Investigational product, dosage, and mode of administration:

Niraparib:

Niraparib will be supplied as CCI [redacted].

For participants randomized to niraparib neoadjuvant treatment, the starting dose will be as follows:

- 200 mg (CCI [redacted]) for participants with an actual body weight <77 kg OR screening platelet count <150 000/µL on Cycle 1 Day 1 (C1D1)
- 300 mg (CCI [redacted]) for participants with an actual body weight ≥77 kg AND screening platelet count ≥150 000/µL on C1D1

For participants receiving niraparib maintenance treatment, independent of the treatment they received during the neoadjuvant treatment period, the starting dose will be as follows:

- 200 mg (CCI [redacted]) for participants with an actual body weight <77 kg OR platelet count <150 000/µL on C1D1 of the niraparib maintenance treatment period (M1D1)

- 300 mg [redacted]) for participants with an actual body weight ≥77 kg AND platelet count ≥150 000/µL on M1D1
- For participants who received niraparib in the neoadjuvant period and experienced niraparib dose reductions due to AEs, the Investigator, in consultation with the Sponsor's Medical Monitor, will determine the safest starting dose in the maintenance setting

Participants will be instructed to take niraparib at the same time each day. Bedtime administration may be a potential method for managing nausea. Participants must swallow and not chew all [redacted] The consumption of water and food is permissible. Niraparib will be dispensed to participants on each scheduled visit until the participant discontinues study treatment. The Study Reference Manual contains descriptions of the packaging of niraparib and instructions for the preparation and administration of niraparib.

Duration of treatment:

Neoadjuvant therapy (niraparib or platinum-taxane doublet chemotherapy) will consist of three 21-day cycles.

Adjuvant therapy (platinum-taxane doublet chemotherapy with optional bevacizumab or bevacizumab biosimilar for participants deemed high-risk) will consist of up to three 21-day cycles, with the last cycle (C6) for all therapies being optional. Any site choosing to give the last cycle and/or bevacizumab or bevacizumab biosimilar must offer the final cycle (C6) to all participants treated at that site regardless of the arm the participant was enrolled onto.

Maintenance treatment with niraparib (with optional bevacizumab or bevacizumab biosimilar for participants deemed high-risk up to a total of 22 cycles including adjuvant chemotherapy period) will continue for up to 36 months.

Participants will continue to receive their assigned treatment until radiographic PD is documented per RECIST v1.1, AE, risk to participant or participant's severe noncompliance with protocol as judged by the Investigator or Sponsor, participant's request, pregnancy, or end of study.

Reference therapy, dosage, and mode of administration:

Carboplatin-paclitaxel:

Carboplatin will be infused intravenously over 60 minutes at the prescribed dose of area under the concentration versus time curve of 5 to 6 mg/mL•min on Day 1 of every 21-day cycle. Paclitaxel will be administered in a similar fashion over 180 minutes at the prescribed dose of 175 mg/m^2 on Day 1 of every 21-day cycle.

Prior to each chemotherapy administration, all of the following criteria must be met: 1) absolute neutrophil count ≥1500/µL or ≥1000/µL if granulocyte colony-stimulating factor is to be administered, 2) platelet count ≥100 000/µL, 3) hemoglobin ≥9 g/dL. For participants who did not tolerate carboplatin-paclitaxel during the run-in period, cisplatin and docetaxel are accepted alternatives.

Bevacizumab or bevacizumab biosimilar (optional):

Bevacizumab or bevacizumab biosimilar 7.5 mg/kg or 15 mg/kg will be infused intravenously on Day 1 of each 21-day cycle. Bevacizumab or bevacizumab biosimilar may be administered for up to 22 cycles during the adjuvant and maintenance periods.

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint is pre-IDS unconfirmed ORR, defined as the percentage of participants with unconfirmed complete or partial response on study treatment pre-IDS as assessed per RECIST v1.1 by the Investigator.

Secondary efficacy endpoints are as follows:

- CA-125 progression by GCIG CA-125 response criteria
- PFS, defined as the time from the date of treatment randomization to the date of first documentation of PD per RECIST v1.1 or death by any cause, whichever occurs first, as determined by the Investigator
- OS, defined as the time from the date of treatment randomization to the date of death by any cause
- TFST, defined as the time from the date of treatment randomization to the date of first subsequent anticancer therapy or death

CCI [redacted]

Safety:

Safety endpoints include frequency and severity of treatment-emergent adverse events, serious adverse events, AESIs, and dose modification (i.e., interruptions and discontinuations).

Other secondary endpoints:

Additional secondary endpoints, include PRO endpoints, arranged in order of clinical importance, are as follows:

- Change over time in frequency and severity of the items on the Patient Reported Outcomes-Common Terminology Criteria for Adverse Events during neoadjuvant treatment
- Change from baseline in Functional Assessment of Cancer Therapy-Item GP5 during neoadjuvant treatment
- Change from baseline in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 items (EORTC Item Library 136) pre-IDS
- Change from baseline in EORTC Quality of Life Questionnaire for OC gastrointestinal items (EORTC Item Library 137) pre-IDS

Biomarkers:

Tumor tissue and/or blood samples may be assessed to identify potential disease- or treatment-related biomarkers that would associate with tumor responses to treatment. Additionally, samples may be assessed to evaluate the evolution of the molecular profile of the tumor and tumor microenvironment in response to treatment.

Pharmacokinetics and Pharmacodynamics:

The pharmacokinetic (PK) endpoints are as follows:

- Residual plasma concentrations of carboplatin and paclitaxel at C1D1
- Niraparib concentration throughout the neoadjuvant treatment period
- Niraparib concentration in tumor tissue from IDS biopsy

Statistical methods:

CCI [redacted]

Enrollment will be stratified by *BRCA* mutational status (*BRCAmut* vs *BRCAwt*/unknown).

Interim analysis:

CCI [redacted]

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADR	Adverse drug reaction; An adverse event where a causal relationship between a medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. a. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). b. For marketed products, ADRs are subject to expedited reporting within the country where they are authorized
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
AML	acute myeloid leukemia
AxMP	auxiliary medicinal product; Medicinal products used in the context of a clinical trial but not as investigational medicinal products, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess endpoints in a clinical trial. AxMPs should not include concomitant medications, this is medications unrelated to the clinical trial and not relevant for the design of the clinical trial. <u>Authorized AxMP</u> Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product. • Safety reporting with regard to auxiliary medicinal products shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC. <u>Unauthorized AxMP</u> Medicinal product not authorized in accordance with Regulation (EC) No 726/2004 • Safety reporting for unauthorized auxiliary medicinal products will follow the same processes and procedures as SUSAR safety reporting
BRCA	breast cancer gene
*BRCA*m/*BRCAmut*	breast cancer gene mutated
CA-125	cancer antigen 125
CBC	complete blood count

Abbreviation or Specialist Term	Explanation
CI	confidence interval
CNS	central nervous system
Co-administered (concomitant) products	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
Comparator	Any product used as reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle x Day x
CYP	cytochrome P450 enzyme
DCR	disease control rate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
EORTC IL136	European Organisation for Research and Treatment of Cancer Item Library 136
EORTC IL137	European Organisation for Research and Treatment of Cancer Item Library 137
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-OV28	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Ovarian Cancer
EOT	End-of-Treatment
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-GP5	Functional Assessment of Cancer Therapy-Item GP5
FDA	Food and Drug Administration
GCIG	Gynecological Cancer InterGroup
GCP	Good Clinical Practice
GSK	GlaxoSmithKline

Abbreviation or Specialist Term	Explanation
HCRU	healthcare resource utilization
HIV	human immunodeficiency virus
HR	hazard ratio
HRD	homologous recombination deficiency
HRd	homologous recombination-deficient
HRp	homologous recombination-proficient
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICU	intensive care unit
IDS	interval debulking surgery
IMP	investigational medicinal product (investigational product); A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
MDS	myelodysplastic syndrome
mPFS	median progression-free survival
MRI	magnetic resonance imaging
MxDx	Cycle x Day x during maintenance treatment period
NACT	neoadjuvant chemotherapy
NCI	National Cancer Institute
NED	no evidence of disease
NIMP	non-investigational medicinal product
non-*BRCA*	breast cancer gene unmutated
NVRD	no visible residual disease
OC	ovarian cancer
ODWG	Organ Dysfunction Working Group

Abbreviation or Specialist Term	Explanation
OPC	Oncology Patient Council
ORR	overall response rate
OS	overall survival
PARP	poly-ADP-ribose polymerase
pCR	pathological complete response
PD	progression of disease
PDS	primary debulking surgery
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PRO-CTCAE	Patient Reported Outcomes-Common Terminology Criteria for Adverse Events
PT	prothrombin time
PTT	partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
Rescue medication	Medicines identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	standard of care; Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. • Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries

Abbreviation or Specialist Term	Explanation
SUSAR	Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting
TFST	time to first subsequent treatment
ULN	upper limit of normal
WOCBP	woman of childbearing potential
WONCBP	woman of non-childbearing potential
WPAI:GH	Work Productivity and Activity Impairment – General Health

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5. INTRODUCTION

An introduction to the overall study is provided in the master protocol. The intent of this cohort is to evaluate the efficacy and safety of neoadjuvant niraparib compared to neoadjuvant platinum-taxane doublet chemotherapy for the treatment of participants with confirmed homologous recombination-deficient (HRd) Stage III to IV ovarian cancer (OC).

5.1. Ovarian Cancer

Epithelial ovarian, fallopian tube, and primary peritoneal cancers are collectively referred to as OC. In the United States, OC is the fifth most common cause of cancer death in women and the most lethal of all gynecologic cancers, with 21 410 new cases of OC estimated to be diagnosed in 2021 and 13 770 women expected to die from this disease [American Cancer Society]. Worldwide, 313 959 new cases of OC and 207 252 deaths were estimated for 2020 [Global Cancer Observatory]. The majority (84%) of OC is diagnosed in advanced stages (III to IV), making the prognosis very unfavorable. The mainstay of OC management includes surgery, chemotherapy, and targeted therapy [Berkenblit, 2005; Hoskins, 1992; Hoskins, 1994; Kehoe, 2015; Burger, 2011]. Generally, primary debulking surgery (PDS) with no visible residual disease (NVRD) followed by adjuvant platinum-taxane doublet chemotherapy offers the best prognosis [Bristow, 2002; van der Burg, 1995; Bristow, 2006; Chang, 2013]. PDS was compared with neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) in 2 international Phase 3 clinical studies, the European Organisation for Research and Treatment of Cancer (EORTC) 55971 study and the CHORUS study [Kehoe, 2015; Vergote, 2010]. Results of these studies demonstrated that the IDS is not inferior to PDS. For both studies, the Grade 3 and Grade 4 postoperative adverse events (AEs) and deaths within 28 days of surgery were significantly more common in the PDS group. A per-protocol pooled analysis of long-term follow-up data for these 2 studies demonstrated that PDS and IDS result in similar overall survival (OS), with better survival with NACT in Stage IV disease [Vergote, 2018]. IDS is therefore considered to be an acceptable alternative to PDS and is a growing practice worldwide for patients with high volume Stage III or IV disease.

5.2. Niraparib

Overall clinical experience with niraparib is summarized in the master protocol and the niraparib Investigator's Brochure (IB) [Niraparib IB].

Niraparib (GSK3985771, formerly MK-4827) is an orally available, potent, highly selective poly-ADP-ribose polymerase (PARP)-1 and PARP-2 inhibitor approved globally for first-line maintenance treatment of OC across various biomarkers. Niraparib has demonstrated activity in participants with HRd (including breast cancer gene [*BRCA*] mutated [*BRCA*m] and *BRCA* unmutated [non-*BRCA*] diseases) and participants with homologous recombination-proficient (HRp) tumors.

In the Phase 3 PRIMA study (ClinicalTrials.gov number NCT02655016), the median progression-free survival (mPFS) in participants with advanced HRd OC who responded to first-line platinum-based chemotherapy was 21.9 months with niraparib and 10.4 months with placebo (hazard ratio [HR] 0.43; 95% confidence interval [CI] 0.31 to 0.59; $p<0.001$). In the overall population (all participants, independent of homologous recombination status), the mPFS was

13.8 months with niraparib and 8.2 months with placebo (HR 0.62; 95% CI 0.50 to 0.76; p<0.001).

In the Phase 3 NOVA study (ClinicalTrials.gov number NCT01847274) in participants with recurrent epithelial OC who responded to second-line platinum-based chemotherapy, the mPFS for niraparib was longer than placebo in the germline *BRCA*m cohort: 21.0 versus 5.5 months (HR 0.27; 95% CI 0.17 to 0.41; p<0.001); longer than placebo in the HRd non-*BRCA* cohort: 12.9 versus 3.8 months (HR 0.38; 95% CI 0.24 to 0.59; P<0.001); and longer than placebo in overall non-*BRCA* cohort: 9.3 versus 3.9 months (HR 0.45; 95% CI 0.34 to 0.61; p<0.001). In both PRIMA and NOVA studies, a continuum of benefit was demonstrated with efficacy in *BRCA*m > HRd > HRp disease.

In addition to approvals by the Food and Drug Administration (FDA) and the European Medicines Agency in the front-line and recurrent maintenance setting for OC, niraparib was also studied for the treatment of women with recurrent OC. In the Phase 2 QUADRA study (ClinicalTrials.gov number NCT02354586), the safety and efficacy of niraparib was evaluated in women with metastatic, relapsed, platinum-sensitive, advanced, HRd OC who have received 3 or more lines of chemotherapy. Consistent with the results in NOVA, a continuum of clinical benefit defined by clinical and molecular biomarkers was shown in the QUADRA study with an overall response rate (ORR) of 28% (95% CI 15.6 to 42.6; one-sided p=0.00053). The mPFS in this tumor HRd population was 5.5 months (95% CI 3.5 to 8.2), and the median duration of response was 9.2 months; 68% achieved disease control (95% CI 53 to 81).

5.3. Other PARP Inhibitors as Treatment for Ovarian Cancer

Niraparib is not the only PARP inhibitor that demonstrated improvements in ORR and PFS as treatment for relapsed OC. In the Phase 3 SOLO3 study (ClinicalTrials.gov number NCT02282020), olaparib demonstrated statistically significant improvements in ORR and PFS as compared with non-platinum chemotherapy in women with platinum-sensitive, relapsed, *BRCA*m OC [Penson, 2020]. ORR and mPFS assessed by blinded independent central review were significantly higher for olaparib than chemotherapy, with an ORR of 72.2% versus 51.4% (odds ratio 2.53; 95% CI 1.40 to 4.58; p=0.002) and mPFS of 13.4 versus 9.2 months (HR 0.62; 95% CI 0.43 to 0.91; p=0.013), respectively. AEs were consistent with expectations. Recently, the Phase 3 ARIEL4 study (ClinicalTrials.gov number NCT02855944) reported positive results for rucaparib showing increased mPFS with rucaparib (7.4 months) compared with standard of care (SOC) chemotherapy (5.7 months; HR 0.639) in women with relapsed, *BRCA*m OC [Kristeleit, 2021].

5.4. Rationale of the Current Cohort

Despite promising results with PDS and IDS, the majority of patients with advanced OC at diagnosis will relapse after initial treatment. Recurrence within 6 months of platinum-based chemotherapy is defined as platinum-resistant disease, which confers a significantly worse prognosis, with median OS reported in clinical studies ranging from less than a year to 19 months. Therefore, OC remains a deadly disease with a poor prognosis for many of the affected women. Improvements in the neoadjuvant therapy resulting in a greater percentage of women with NVRD at IDS is expected to translate into better survival outcomes. Niraparib is an

active oral agent and has the potential to minimize or even replace the use of intravenous cytotoxic chemotherapy in the neoadjuvant setting.

With PARP inhibitors moving into the front-line setting, there is a need to understand the evolution of the molecular landscapes of the tumor and its associated tumor microenvironment following PARP inhibitor treatment, in order to generate insights to develop rationale for future treatment combinations aiming to broaden and deepen treatment responses. Neoadjuvant therapy settings offer unique sampling opportunities pre- and post-PARP inhibitor treatment that will enable exploratory translational research.

Therefore, the aim for this cohort is to evaluate the efficacy, safety, and tolerability of neoadjuvant niraparib compared with neoadjuvant platinum-taxane doublet chemotherapy after one induction cycle of platinum-taxane doublet chemotherapy in participants with advanced OC. Given the continuum of benefit demonstrated with niraparib, participants with advanced OC with HRd tumors will be enrolled in Cohort C.

5.5. Benefit/Risk Assessment

Niraparib, a once daily oral treatment, prolonged the effect of platinum-based chemotherapy, substantially improved PFS and significantly reduced the risk of recurrence or death in a broad OC population of patients; thereby enabling a delay in disease recurrence and the need for additional platinum-based or other chemotherapy with its associated cumulative toxicities as demonstrated in multiple clinical trials (see [Niraparib IB]).

The AE profile of niraparib consisted of AEs that are commonly managed in the patient population with advanced cancer. The key safety concerns included hematological toxicities, hypertension, MDS/AML, and potential risks of secondary malignancies. Common AEs including Grade 3 and higher AEs were generally manageable with dose modification and clinical treatment; most of which resolved without discontinuation of study drug.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of niraparib may be found in the prescribing information (SmPC, USPI) and in the latest edition of the niraparib IB. Detailed information about the benefit-risk and expected AEs for carboplatin, paclitaxel, and bevacizumab (or bevacizumab biosimilar) may be found in the respective package inserts/prescribing information.

Overall, the benefit-risk profile of niraparib is anticipated to be favorable in the population for Study 213357. The risk mitigation strategies are implemented in the study protocol. The Sponsor will continue to closely monitor the available safety data for known and emergent risks.

6. TRIAL OBJECTIVES AND PURPOSE

The following are the cohort-specific objectives for this study, which have been further specified from the overall study objectives presented in the master protocol.

6.1. Primary Objective

- To evaluate the efficacy of neoadjuvant niraparib compared with neoadjuvant platinum-taxane doublet chemotherapy after 1 induction cycle of carboplatin-paclitaxel per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in participants with confirmed HRd Stage III to IV OC

6.2. Secondary Objectives

- To evaluate clinical benefit by Gynecological Cancer InterGroup (GCIG) cancer antigen 125 (CA-125) response criteria
- To evaluate clinical benefit as measured by progression-free survival (PFS) per RECIST v1.1 by investigator assessment
- To evaluate participants' reported overall tolerability toward treatment, overall health status, OC-specific health-related quality of life (HRQoL) and symptoms, and work productivity
- To evaluate clinical benefit as measured by OS
- To evaluate clinical benefit as measured by time to first subsequent treatment (TFST)
- To evaluate the safety and tolerability of neoadjuvant niraparib and neoadjuvant platinum-taxane doublet chemotherapy

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7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

The overall study design is described in the master protocol.

This is a global, multicenter, randomized, open-label, Phase 2 cohort in participants with newly diagnosed, Stage III or IV, high-grade non-mucinous epithelial ovarian, fallopian tube, or peritoneal cancer (collectively referred to as "ovarian cancer" or OC) who are eligible for neoadjuvant platinum-taxane doublet chemotherapy followed by IDS. This study will enroll participants with HRd OC as determined by the central tumor homologous recombination deficiency (HRD) testing using a fully validated assay. All prescreened participants would have received, prior to enrollment, 1 cycle of SOC chemotherapy (i.e., carboplatin-paclitaxel) to allow sufficient time for receipt and review of the biomarker test results. After confirmation that the tumor is HRd, participants will be randomized in a 1:1 ratio to 3 cycles of platinum-taxane doublet chemotherapy (carboplatin-paclitaxel, unless not tolerated by the participant; Arm 1) or 3 cycles of neoadjuvant niraparib (Arm 2).

After IDS, all participants will receive up to three 21-day cycles of adjuvant chemotherapy (Cycles 4, 5, and 6) treatment: platinum-taxane doublet chemotherapy (and optional bevacizumab or bevacizumab biosimilar per SOC for participants deemed high-risk as judged by the Investigator), with the last cycle of chemotherapy (C6) being optional. Any site choosing to give the last cycle (C6) for all therapies must offer the final cycle (C6) to all participants treated at that site regardless of the arm the participant was enrolled onto.

After adjuvant chemotherapy treatment, all participants will receive niraparib maintenance treatment (with optional bevacizumab or bevacizumab biosimilar as SOC for up to 22 cycles including adjuvant chemotherapy period) for up to 36 months or until AE, progression of disease (PD) per RECIST v1.1, risk to participant or participant's severe noncompliance with protocol as judged by the Investigator or Sponsor, participant's request, pregnancy, or end of study.

Participants may discontinue treatment for any reason. All participants will undergo an End-of-Treatment (EOT) Visit within 7 days after the last dose of study treatment or at the time of PD per RECIST v1.1, whichever occurs first. Participants who discontinue study treatment due to treatment toxicity or intolerability prior to an investigator assessment of PD per RECIST v1.1 will continue radiographic imaging until PD per RECIST v1.1, start of alternate anticancer therapy, participant discontinuation of the study, withdrawal of consent to study procedures, becoming lost to follow-up, death, or end of the study.

A Safety Follow-up Visit will be conducted 30 days (±7 days) after the last dose of study treatment. After the 30-day (±7 days) Safety Follow-up Visit, all participants will enter the long-term follow-up period of telephone assessment for survival status, assessment of subsequent anticancer therapy, and the occurrence of any adverse event of special interest (AESI) every 90 days (±14 days) until participant discontinuation of the study, withdrawal of consent, death, or end of study.

Radiographic imaging will continue as scheduled during the posttreatment follow-up period for all participants without PD per RECIST v1.1 at treatment discontinuation until PD per RECIST v1.1, start of alternate anticancer therapy, participant discontinuation of the study,

withdrawal of consent to study procedures, becoming lost to follow-up, death, or end of the study.

The study duration for each participant will be up to approximately 43 months. The study will be divided in 5 periods: overall screening (Prescreening and Screening), neoadjuvant treatment, IDS, adjuvant chemotherapy treatment, and niraparib maintenance. The study periods are described in more detail in Section 7.1.1 through Section 7.1.5. The Cohort C study schema is provided in Figure 2.

The visit frequency is every 3 weeks in the neoadjuvant and adjuvant treatment periods and during the first 13-14 months in the niraparib maintenance treatment period (depending on whether participants will be offered 3 or 2 cycles of adjuvant chemotherapy, respectively). Subsequently, the visit frequency will change to every 3 months for the remainder of the niraparib maintenance treatment period. An overview of study procedures and the timing of assessments are provided in Section 7.6.

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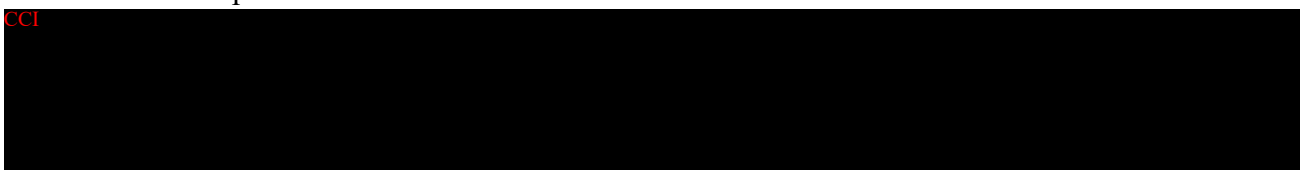


To safeguard the interest and safety of the participants in this cohort, a GSK Data Review Committee, independent of the GSK study team directly involved in the conduct of the trial will be used to conduct review of incoming data to monitor efficacy and emerging safety signals. The panel may recommend modifications to the design of the protocol or discontinuation of the cohort, if necessary.

7.1.1. Overall Screening Period

The overall screening period will include Prescreening and Screening periods and be approximately 6 weeks.

7.1.1.1. Prescreening

Prior to main study enrollment, a Prescreening period of approximately 5 weeks is required to ensure that all potential participants meet preliminary eligibility criteria and have tumor tissue testing and baseline assessments (including blood sampling to evaluate complete blood counts for study eligibility), if not already done, performed consistent with the protocol. Participants must sign a Prescreening informed consent form (ICF) documenting their agreement for collection and submission of the required central tumor tissue and blood samples for biomarker analysis (central HRD testing for eligibility and tissue- and blood-based exploratory biomarker testing). Adequate tissue and other biologic specimens are required to proceed to randomization and enrollment in the study. Given the urgency of commencing treatment and the timeline for return of central HRD testing results to determine study eligibility, participants are expected to receive 1 run-in cycle of carboplatin-paclitaxel in accordance with local SOC treatment prior to enrollment in the study.

7.1.1.2. Screening

Following recovery from the run-in cycle of carboplatin-paclitaxel (up to 5 weeks), participants who have confirmed tumor HRd status and signed an ICF will have their eligibility criteria confirmed after the complete review of inclusion and exclusion criteria, including confirmation that the participant will provide tumor tissue for exploratory biomarker testing (if not already done so during Prescreening) over a 1-week period. The screening procedures include, but are not limited to, hematology, chemistry, CA-125, ECG, and a RECIST v1.1 scan. The RECIST v1.1 scan, performed after the run-in cycle of carboplatin-paclitaxel, will be considered the baseline scan.

7.1.2. Neoadjuvant Treatment Period

After completing the screening procedures, participants will be randomized in a 1:1 ratio to platinum-taxane doublet chemotherapy (carboplatin-paclitaxel, unless not tolerated; Arm 1) or daily niraparib (Arm 2) for three 21-day cycles. Randomization will be stratified by *BRCA* mutational status (*BRCAmut* vs *BRCAwt*/unknown).

Participants can start Cycle 1 Day 1 (C1D1) following recovery from the run-in cycle of carboplatin-paclitaxel. C1D1 is to occur up to 5 weeks after Day 1 of administration of the run-in cycle of carboplatin-paclitaxel. For details on study drug administration, see Section 10.5.

After completion of 3 cycles of neoadjuvant therapy (i.e., NACT or niraparib), participants will undergo a pre-IDS assessment per RECIST v1.1 by the Investigator. The pre-IDS assessments should begin after completion of the final cycle of neoadjuvant therapy and up to 2 weeks prior to IDS. The neoadjuvant treatment period, from C1D1 to IDS, can be up to 12 weeks. Criteria for selecting participants for IDS are outlined in Figure 1.

Participants with unconfirmed complete response (CR) or unconfirmed partial response (PR) according to RECIST v1.1 will proceed to IDS to be performed by a qualified gynecological/surgical oncologist, with the aim of achieving NVRD. Participants with stable disease (SD) per RECIST v1.1 may proceed to IDS or alternative therapy at the Investigator's discretion. Surgical and postsurgical outcomes will be collected. Postsurgical safety will be assessed according to local SOC for 30 days (± 7 days) after IDS and before adjuvant chemotherapy. Participants with PD will discontinue study treatment and proceed to an alternative therapy at the Investigator's discretion.

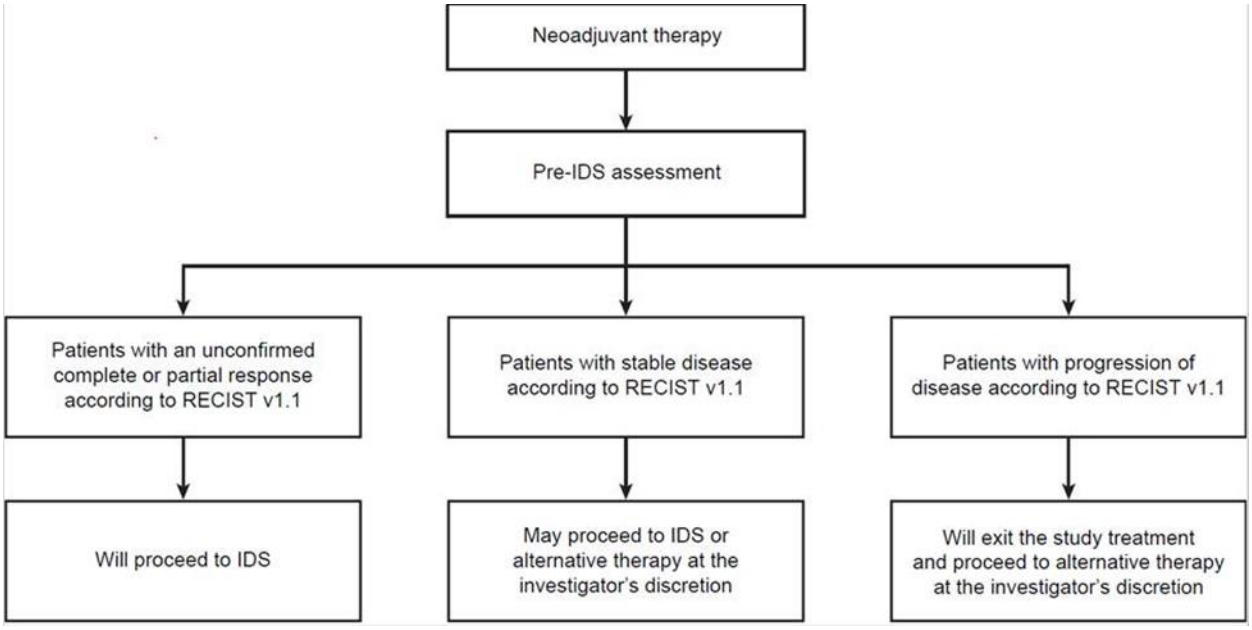
Clinical progression as determined by signs, symptoms, physical examination results, or increased CA-125 (≥15% from nadir) are not acceptable reasons for neoadjuvant treatment discontinuation but may trigger an additional scan for RECIST v1.1 evaluation. If the participant does not meet SD or PD per RECIST v1.1 but the Investigator believes that it is in the best interest of the participant to discontinue neoadjuvant treatment, the treatment may be discontinued after discussion with the Medical Monitor for this cohort. The additional scan performed for this evaluation will be used for the primary efficacy analysis.

Participants who discontinue treatment for reasons other than PD per RECIST v1.1 should continue to be scanned until RECIST v1.1 PD or start of alternate therapy.

Participants who receive additional cycle(s) of platinum-taxane doublet chemotherapy prior to IDS, when clinically indicated, will be considered as having discontinued treatment and must

provide imaging per RECIST v1.1 after 3 cycles of on-study neoadjuvant therapy and undergo procedures as per EOT.

Figure 1: Criteria for Selecting Participants for IDS



Pre-IDS assessment per RECIST v1.1 by the Investigator will occur after completion of 3 cycles of neoadjuvant therapy (i.e., NACT or niraparib). Pre-IDS assessments should begin after completion of the final cycle of neoadjuvant therapy and up to 2 weeks prior to IDS.

7.1.3. IDS Period

Participants who have unconfirmed CR or unconfirmed PR per RECIST v1.1 at their pre-IDS tumor evaluation (pre-IDS assessments are outlined in Section 7.1.2) will undergo IDS by a trained gynecologic/surgical oncologist with the aim of maximum surgical effort toward NVRD. IDS will be performed after the final cycle of neoadjuvant therapy; approximately 3 to 6 weeks after C3D1. The IDS period, from IDS to C4D1, can take up to 6 weeks. Surgical and postsurgical outcomes will be collected during this period.

Participants will undergo postsurgical safety evaluations per local SOC for up to 30 days after IDS and prior to the start of adjuvant chemotherapy. Participants who experience PD per RECIST v1.1 should discontinue study treatment and proceed to alternative therapy at the Investigator's discretion.

7.1.4. Adjuvant Chemotherapy Treatment Period

Per standard practice, platinum-taxane doublet chemotherapy is given for more than 4 cycles. Therefore, after surgical recovery (up to 6 weeks), all participants randomized to neoadjuvant platinum-taxane doublet chemotherapy (Arm 1) will receive up to 3 additional 21-day cycles of platinum-taxane doublet chemotherapy (and optional bevacizumab or bevacizumab biosimilar as SOC for participants deemed high-risk as determined by the Investigator); Cycle 6 is optional. If a site chooses to administer a third cycle of platinum-taxane doublet chemotherapy (and optional bevacizumab or bevacizumab biosimilar for participants deemed high-risk), all participants

treated at this study site must be offered the third cycle (Cycle 6) of platinum-taxane doublet chemotherapy (and optional bevacizumab or bevacizumab biosimilar for participants deemed high-risk), regardless of treatment received during the neoadjuvant treatment period.

In order to balance the 2 treatment arms, all participants randomized to neoadjuvant niraparib (Arm 2) will also receive up to three 21-day cycles of platinum-taxane doublet chemotherapy (and optional bevacizumab or bevacizumab biosimilar for participants deemed high-risk) after surgical recovery (up to 6 weeks; Cycle 6 is optional).

The adjuvant chemotherapy treatment period will take up to approximately 6 to 9 weeks.

7.1.5. Maintenance Treatment Period

To assess disease status following adjuvant chemotherapy, diagnostic imaging per RECIST v1.1 will be performed within 14 days prior to Cycle 1 Day 1 of the maintenance treatment period (M1D1). Participants who completed the adjuvant chemotherapy period without PD per RECIST v1.1 will start the niraparib (and optional bevacizumab or bevacizumab biosimilar for participants deemed high-risk) maintenance treatment in cycles of 3 weeks. The start of maintenance treatment can be delayed at least 6 weeks and up to 9 weeks after C5D1 (or C6D1 if a third cycle of adjuvant chemotherapy therapy was received) to allow for adequate recovery of hematologic and nonhematologic toxicity. Maintenance treatment will be up to 36 months (including 22 cycles of optional bevacizumab or bevacizumab biosimilar starting in adjuvant chemotherapy period) or until AE, PD per RECIST v1.1, risk to participant or participant's severe noncompliance with protocol as judged by the Investigator or Sponsor, participant's request, pregnancy, or end of study.

Maintenance imaging assessments will start at M1D1 or within 14 days prior to M1D1. Additional assessments will be performed every 3 months (±7 days) for 1 year after M1D1, followed by every 6 months (±14 days) during the second year, and every year thereafter until PD per RECIST v1.1, start of alternate anticancer therapy, participant discontinuation of the study, withdrawal of consent to study procedures, becoming lost to follow-up, death, or end of the study. Additional unscheduled RECIST v1.1 computed tomography (CT) or magnetic resonance imaging (MRI) scans may be performed if the participant has increasing CA-125 values or suspicious symptoms.

7.1.6. End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Events (Table 5) for the last participant in the study globally.

A participant will be considered to have completed the study if the participant dies during the Intervention Period or Follow-up Period, or has been in follow-up for up to 4 years after enrollment of the last participant, whichever is sooner. The cause of death must be documented in the eCRF. In addition, participants who are receiving ongoing study intervention or are in the follow-up period at the time of the Sponsor's decision to close the study will be considered to have completed the study. A participant will be considered to have withdrawn from the study if the participant has not died and is lost to follow-up, has withdrawn consent, or is no longer being followed at the Investigator's discretion.

Participants who continue to derive benefit from niraparib in the opinion of the Investigator, may be provided an option to continue to receive niraparib under an extension study, rollover study, expanded access, or other program, as applicable.

Figure 2: Cohort C Study Schema

Note: Duration of study periods are as follows:
Prescreening: 5 weeks
Screening: 1 week
Neoadjuvant treatment: up to 12 weeks
IDS: up to 6 weeks
Adjuvant platinum-taxane chemotherapy and optional bevacizumab or bevacizumab biosimilar: 6 to 9 weeks*
Niraparib maintenance: up to 36 months. Optional bevacizumab or bevacizumab biosimilar may be administered for up to 22 cycles (including adjuvant chemotherapy period).

*Note: Cycle 6 is optional. If a site chooses to administer cycle 6 (C6) of adjuvant chemotherapy, all participants treated at this study site must be offered C6 of adjuvant chemotherapy, regardless of treatment received during the neoadjuvant treatment period. Any site that chooses to provide optional bevacizumab or bevacizumab biosimilar as SOC to eligible high-risk participants must offer it to all eligible high-risk participants treated at that site, regardless of enrollment arm.

Stratification: *BRCAmut* (deleterious or suspected deleterious *BRCA1* or *BRCA2* mutation) vs *BRCA*wt/unknown (no deleterious or suspected deleterious *BRCA1* or *BRCA2* mutation; including unknown)

Abbreviations: *BRCA*=breast cancer gene; *BRCAmut*=*BRCA* mutant; *BRCA*wt=*BRCA* wildtype; C=cycle; carbo=carboplatin; chemo=chemotherapy; CR=complete response; Cx=cycle number; endpt=endpoint; EU=European Union; HR=homologous recombination; HRd=homologous recombination-deficient; ICF=informed consent form; IDS=interval debulking surgery; mPFS=median progression-free survival; NVRD=no visual residual disease; ORR=overall

response rate; OS=overall survival; pathCR=pathological complete response; PD=pharmacodynamics; PFS=progression-free survival; PK=pharmacokinetics; PRO=patient-reported outcome; QD=once daily; R=randomization; SOC=standard of care; TFST=time to first subsequent treatment; xxm=xx months.

7.2. Number of Participants

CCI [redacted]

7.3. Treatment Assignment

Participants enrolled in this cohort will be randomized in a 1:1 ratio to 3 cycles of neoadjuvant platinum-taxane doublet chemotherapy (carboplatin-paclitaxel, unless not tolerated by the participant; Arm 1) or 3 cycles of neoadjuvant niraparib (Arm 2). After IDS, all participants will receive up to three 21-day cycles of adjuvant platinum-taxane doublet chemotherapy (and optional bevacizumab for participants deemed high-risk); third cycle is optional followed by niraparib (and optional bevacizumab or bevacizumab biosimilar for participants deemed high-risk) maintenance treatment.

7.4. Dose Adjustment Criteria

7.4.1. Safety Criteria for Adjustment or Stopping Doses

Dosing regimens for niraparib, carboplatin-paclitaxel, and optional bevacizumab or bevacizumab biosimilar are described in Section 7.1.

7.4.1.1. Niraparib

Niraparib Dose Interruption and Modification

Dose interruption, no longer than 28 days during the neoadjuvant and maintenance treatment periods, or dose reduction will be allowed based on treatment side effects. For participants whose initial dose is 300 mg/day (CCI [redacted]), dose reductions to 200 mg/day CCI [redacted] and subsequently to 100 mg/day CCI [redacted]) will be allowed. For participants whose initial dose is 200 mg/day CCI [redacted]), dose reduction to 100 mg/day (CCI [redacted] will be allowed.

Treatment must be interrupted for any nonhematologic Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or Grade 4 AE that the Investigator considers to be related to administration of niraparib (Table 3). If the nonhematologic toxicity is appropriately resolved to baseline or Grade ≤1 within 4 weeks (28 days) of the dose interruption period, the participant may restart treatment with niraparib but with a dose level reduction if prophylaxis is not considered feasible (see Table 2). If the event recurs at a similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made. No more than 2 dose reductions will be permitted (i.e., to a minimum dose of 100 mg once daily).

If the toxicity requiring dose interruption has not resolved completely or to CTCAE Grade 1 during the maximum 4-week (28 days) dose interruption period, or the participant has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg once daily), the participant must permanently discontinue treatment with niraparib.

The dose interruption and modification criteria for niraparib for hematologic parameters will be based on blood counts and are outlined in Table 4. If the hematologic toxicity has not recovered to the specified levels within 4 weeks (28 days) of the dose interruption period, or the participant

has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg once daily), the participant must permanently discontinue treatment with niraparib.

Table 2: Niraparib Dose Reductions for Hematologic and Nonhematologic Toxicity

	Body weight <77 kg OR screening platelet count <150 000/µL	**Body weight ≥77 kg AND screening platelet count ≥150 000/µL**
Starting dose	200 mg/day CCI	300 mg/day CCI
First dose reduction	100 mg/day CCI	200 mg/day (CCI
Second dose reduction	Discontinue medication.	100 mg/day[a] (CCI

[a] If further dose reduction below 100 mg/day is required, discontinue niraparib.

Table 3: Niraparib Dose Modifications for Nonhematologic Toxicity

Abnormality	**Intervention**
Nonhematologic CTCAE Grade ≥3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	Withhold niraparib for a maximum of 28 days (neoadjuvant and maintenance periods) or until resolution of adverse reaction. Resume niraparib at a reduced dose per Table 2. Up to 2 dose reductions are permitted for the starting dose of 300 mg; only 1 dose reduction is permitted for the starting dose of 200 mg.
CTCAE Grade ≥3 treatment-related adverse reaction lasting more than 28 days while patient is administered niraparib 100 mg/day	Discontinue niraparib.

Abbreviation: CTCAE=Common Terminology Criteria for Adverse Events.

Table 4: Niraparib Dose Modifications for Hematologic Toxicity

Laboratory Abnormality	Intervention
Monitor complete blood counts weekly for the first cycle and once every treatment cycle thereafter.	
Platelet count <100 000/µL	First occurrence: Withhold niraparib for a maximum of 28 days (neoadjuvant and maintenance periods) and monitor blood counts weekly until platelet counts return to ≥100,000/µL. Resume niraparib at same or reduced dose.[a] If platelet count is <75 000/µL, resume niraparib at a reduced dose.[b]
	Second occurrence: Withhold niraparib for a maximum of 28 days (neoadjuvant and maintenance periods) and monitor blood counts weekly until platelet counts return to ≥100 000/µL. Resume niraparib at a reduced dose.[a] Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days (neoadjuvant and maintenance periods) of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Neutrophil count <1000/µL	Withhold niraparib for a maximum of 28 days (neoadjuvant and maintenance periods) and monitor blood counts until neutrophil counts return to ≥1 500/µL. Resume niraparib at a reduced dose.[a] Discontinue niraparib if neutrophil level has not returned to acceptable levels within 28 days (neoadjuvant and maintenance periods) of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD. Note: Prophylactic cytokines (i.e., granulocyte colony-stimulating factor) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current ASCO guidelines.
Hemoglobin ≤8 g/dL	Withhold niraparib for a maximum of 28 days (neoadjuvant and maintenance periods) and monitor blood counts until hemoglobin returns to ≥9 g/dL. Resume niraparib at a reduced dose.[a] Discontinue niraparib if hemoglobin has not returned to acceptable levels within 28 days (neoadjuvant and maintenance periods) of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Hematologic adverse reaction requiring transfusion	For patients with platelet count ≤10 000/µL, platelet transfusion should be considered. If there are other risk factors for bleeding such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs or transfusion at a higher platelet count. Red blood cell transfusion may be given at the discretion of the Investigator. Resume niraparib at a reduced dose.[a]

Laboratory Abnormality	Intervention
Confirmed diagnosis of MDS or AML	Permanently discontinue niraparib.

Abbreviation: AML=acute myeloid leukemia; ASCO=American Society of Clinical Oncology; MDS = myelodysplastic syndrome; QD = once daily.

[a] Niraparib dose must not be decreased below 100 mg daily. Additional details on dose reduction are described in Table 2.

[b] If platelet count is <75 000/µL at any time, resume niraparib at a reduced dose.

If dose interruption or modification is required at any point during study treatment because of hematologic toxicity, weekly blood draws for complete blood count (CBC) will be monitored until the AE resolves to the specified blood count levels. To ensure the safety of the new dose, weekly blood draws for CBC will be required for an additional 4 weeks after the AE has resolved, after which monitoring every treatment cycle may resume. Based on individual laboratory values, weekly monitoring for the second month may be warranted. Also see Table 5.

Any participant requiring transfusion of platelets or red blood cells (≥1 unit) must undergo a dose reduction upon recovery if study treatment is resumed.

If a diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) is confirmed by a hematologist, the patient must permanently discontinue study treatment.

For major surgery while on study treatment, study treatment interruption is allowed up to up to 4 weeks (28 days) during the neoadjuvant and maintenance treatment periods.

Once the dose of study treatment has been reduced, any re-escalation must be discussed with the Sponsor's Medical Monitor.

All dose interruptions and reductions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded in the electronic case report form (eCRF). Reasons for the discontinuation of niraparib must also be recorded in the electronic case report form.

Hypertension, Including Hypertensive Crisis

Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Pre-existing hypertension should be adequately controlled before starting niraparib treatment. While receiving treatment, hypertension should be medically managed with antihypertensive medicinal products with or without niraparib dose adjustment. BP and heart rate is to be monitored as outlined in Table 5.

Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

Posterior Reversible Encephalopathy Syndrome

There have been rare reports of niraparib-treated participants developing signs and symptoms that are consistent with posterior reversible encephalopathy syndrome (PRES). PRES is a rare, reversible neurologic disorder that can present with the following signs and symptoms: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging,

preferably MRI. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib. The safety of reinitiating niraparib therapy in participants previously experiencing PRES is not known.

Lifestyle and/or Dietary Restrictions

Cases of photosensitivity have been reported for participants on niraparib treatment. Participants must be informed on measures to decrease exposure to ultraviolet light, such as minimizing time under direct sunlight, unless wearing hats and long-sleeves, and application of sun protection creams.

7.4.1.2. Platinum-Taxane Doublet Chemotherapy

Dose modifications and supportive care for platinum-taxane doublet chemotherapy will follow guidelines provided in the prescribing information for each agent or local SOC.

7.4.1.3. Bevacizumab or Bevacizumab Biosimilar

Dose modifications and supportive care for bevacizumab will follow guidelines provided in the prescribing information or local SOC. Key supportive care considerations are provided below.

Restrictions:

- Do not start bevacizumab or bevacizumab biosimilar for at least 28 days following major surgery and until adequate wound healing
- Do not administer bevacizumab or bevacizumab biosimilar to a participant with recent history of hemoptysis
- Do not administer bevacizumab or bevacizumab biosimilar to a participant with uncontrolled hypertension
- Do not administer bevacizumab or bevacizumab biosimilar to a participant with OC with evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on a CT scan or clinical symptoms of bowel obstruction

Precautions:

- Monitor proteinuria by dipstick urine analysis prior to each bevacizumab or bevacizumab biosimilar infusion for the development or worsening of proteinuria with serial urinalyses during bevacizumab or bevacizumab biosimilar therapy. Participants with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Bevacizumab or bevacizumab biosimilar treatment should be withheld for proteinuria greater than or equal to 2 grams per 24 hours and resumed when less than 2 grams per 24 hours. Bevacizumab or bevacizumab biosimilar treatment should be discontinued in participants who develop nephrotic syndrome.
- Bevacizumab or bevacizumab biosimilar treatment should be discontinued for participants who develop gastrointestinal perforation, tracheoesophageal fistula or any Grade 4 fistula, and fistula formation involving any internal organ.
- Monitor blood pressure every 2 to 3 weeks during bevacizumab or bevacizumab biosimilar treatment. Continue to monitor blood pressure at regular intervals in patients

with bevacizumab-induced or bevacizumab-exacerbated hypertension after discontinuation.

7.4.2. Pharmacokinetic Criteria for Adjustment or Stopping Doses

Not applicable.

7.5. Criteria for Cohort Termination

In addition to the criteria for study termination as described in the master protocol, this cohort may be terminated based on the results of the planned interim analysis for futility (Section 13.2.5).

7.6. Study Conduct

7.6.1. Schedule of Events

The schedule of study procedures is provided in Table 5.

7.6.2. Treatment Cycles

Cycles 1 through 6 (neoadjuvant and adjuvant treatment periods) and all remaining cycles (maintenance treatment period) are 21 days (±3 days) long. Visits should occur within ±3 days of the scheduled visit as outlined in Table 5, except for visits C1D8 and C1D15, which should occur within ±1 day.

All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 PM).

7.6.3. Evaluation of Tumor Response

7.6.3.1. RECIST V1.1

All participants are required to undergo radiographic evaluation throughout the study as described in Table 5. Details on the evaluation of tumor response per RECIST v1.1 are provided in the master protocol.

Radiographic evaluations to assess extent of disease will be conducted as follows:

- Overall Screening Period: during Screening after the run-in cycle of carboplatin-paclitaxel and within 7 days immediately prior to C1D1 (i.e., baseline RECIST v1.1 scan)
- Neoadjuvant Treatment Period: after completion of 3 cycles of neoadjuvant therapy (i.e., pre-IDS assessment), up to 2 weeks prior to IDS
- Maintenance Treatment Period: at M1D1 or within 14 days prior to M1D1, every 3 months (±7 days) for 1 year after M1D1, every 6 months (±14 days) during the second year, and every year thereafter
- Radiographic evaluations, for participants on treatment and participants who discontinued treatment for reasons other than PD per RECIST v1.1, will continue until PD per RECIST v1.1, start of alternate anticancer therapy, participant

discontinuation of the study, withdrawal of consent to study procedures, becoming lost to follow-up, death, or end of the study.

- As surgery is considered as part of the treatment paradigm of this study, if a participant has no visible lesion on the pre-maintenance scan, the overall response will be defined as CR. If a participant has visible lesion(s) on the pre-maintenance scan, the overall response will be defined as PR or SD depending on the extent of the disease compared to the baseline (Screening) scan. There will be no censoring as a result of the removal of the lesion(s) identified at Screening during IDS.

7.6.3.2. GCIG CA-125 Response Criteria

Serum samples to evaluate CA-125 will be taken throughout the study (Table 5). GCIG CA-125 response criteria will be used to determine CA-125 progression [Rustin, 2004]. PD will not be diagnosed in case of CA-125 progression in the absence of radiologic evidence of PD per RECIST v1.1.

7.6.3.3. Pathological Complete Response

CCI [redacted]

7.6.4. Overall Survival

Survival status will be collected for all participants until up to 4 years after the enrollment of the last participant, provided that this allows the collection of sufficient OS events.

7.6.5. Time to First Subsequent Treatment

Survival status and subsequent anticancer therapy assessment will be evaluated for all participants until up to 4 years after the enrollment of the last participant.

7.6.6. Patient-reported Outcome Questionnaires

Participants will complete the following patient-reported outcome (PRO) and work productivity questionnaires as per Schedule of Events prior to any other study procedures:

- Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) – weekly during the neoadjuvant treatment period and at EOT Visit
- Work Productivity and Activity Impairment – General Health (WPAI:GH) questionnaire – weekly during the neoadjuvant treatment period and at EOT Visit
- European Organisation for Research and Treatment of Cancer Item Library 136 (EORTC IL136) (a subset of items from the EORTC Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]) – at site visits during the neoadjuvant and maintenance treatment periods and at EOT Visit
- European Organisation for Research and Treatment of Cancer Item Library 137 (EORTC IL137) (a subset of items from the EORTC Quality of Life Questionnaire for OC [EORTC QLQ-OV28]) – at site visits during the neoadjuvant and maintenance treatment periods and at EOT Visit

- Functional Assessment of Cancer Therapy-Item GP5 (FACT-GP5) – weekly during the neoadjuvant treatment period, at site visits during the maintenance treatment period, and at EOT Visit

The PROs will be administered to participants in different regions based on the availability of translated versions. PROs that are done weekly will be done at home by the participant on a provisioned device, the remaining PROs will be done at the site.

7.6.6.1. PRO-CTCAE

Descriptive data will be presented using items from the PRO-CTCAE as a secondary endpoint. The PRO-CTCAE is a PRO measure developed to evaluate symptomatic toxicity in participants of cancer clinical studies [Basch, 2014]. The PRO-CTCAE was designed to be used as a companion to the CTCAE, the standard lexicon for AE reporting in cancer studies. The PRO-CTCAE includes an item library of 124 items representing 78 symptomatic toxicities drawn from the CTCAE. The PRO-CTCAE provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in cancer clinical studies. In the present study, a selection of items from the PRO-CTCAE Version 1.0 Item Library will be administered to participants (see Study Reference Manual for further details).

A subset of items from the PRO-CTCAE will be assessed. Symptoms for inclusion in the PRO-CTCAE are the following:

- Taste changes
- Nausea
- Vomiting
- Abdominal pain
- Bloating
- Constipation
- Diarrhea
- Concentration
- Memory
- Muscle pain
- Joint pain
- Fatigue
- Anxiety
- Neuropathy
- Sadness

7.6.6.2. FACT-GP5

The change from baseline in the FACT-GP5 will be assessed as a secondary endpoint. The Functional Assessment of Cancer Therapy–- General (FACT-G) (now in Version 4) is a 27-item compilation of general questions divided into 4 primary quality of life domains: physical well-being, social/family well-being, emotional well-being, and functional well-being [Cella, 1993].

The FACT-GP5, a single item from the FACT-G that assesses how bothersome the side effects of treatment are for patients with cancer, will be the only question used for this cohort. The recall period is the past 7 days, and the item has a 5-category response scale ranging from "0=Not at all" to "4=Very much." This item is being included to assess the overall tolerability of treatment from the participant's perspective.

7.6.6.3. EORTC IL136 (a Subset of Items from EORTC QLQ-C30)

The EORTC QLQ-C30 was developed to assess the quality of life of patients with cancer, and it is the most widely used cancer-specific HRQoL instrument.

The EORTC QLQ-C30 is a 30-item questionnaire used to measure HRQoL in participants with cancer; it has been translated and validated in over 100 languages and has been used in more than 3000 studies worldwide [EORTC]. The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 3 symptom scales (fatigue, nausea and vomiting, and pain), 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health status/HRQoL scale. The EORTC QLQ-C30 uses a 1-week recall period for all items and a 4-point scale for the functional and symptom scales/items with response categories of "Not at all," "A little," "Quite a bit," and "Very much." The 2 items assessing global health status/quality of life utilize a 7-point scale ranging from 1 ("Very Poor") to 7 ("Excellent") [Aaronson, 1993].

Select domains from the EORTC QLQ-C30 will be administered and will be referred to as the EORTC IL136. The EORTC IL136 will include the following items:

- Global health status/HRQoL scale
- Functional scale of physical functioning
- Functional scale of social functioning
- Single item of dyspnea

The change from baseline in EORTC IL136 pre-IDS will be assessed as a secondary endpoint.

7.6.6.4. EORTC IL137 (a Subset of Items from EORTC QLQ-OV28)

The OC module (QLQ-OV28) supplements the QLQ-C30 and was designed for patients with local or advanced disease who receive treatment by surgery with or without chemotherapy. It was developed according to the EORTC guidelines. It consists of 28 items and includes 3 functional scales (body image, sexuality, and attitude to disease/treatment burden) and 5 symptom scales/items (abdominal/gastrointestinal symptoms, peripheral neuropathy, hormonal/menopausal symptoms, other chemotherapy side effects, and hair loss).

The scoring approach for the OC module is identical in principle to that used for the scales/items of the EORTC QLQ-C30.

A subset of the questions (9 questions) will be utilized for this cohort and will be referred to as the EORTC IL137. The change from baseline in EORTC IL137 pre-IDS will be assessed as a secondary endpoint.

7.6.6.5. WPAI:GH

The WPAI:GH consists of 6 questions that elicit the following: employment status; hours missed due to health problems; hours missed due to other reasons; hours actually worked; and 2 questions that measure the degree of health problems affecting productivity while working (presenteeism) and regular daily activities, on a scale from 0 to 10. Scores for absenteeism, presenteeism, overall work productivity loss (combined absenteeism plus presenteeism), and impairment in regular daily (nonwork) activities, such as work around the house, shopping, child care, exercising, studying, etc., are derived for the interval of the past 7 days; scores are expressed as percent of impairment/productivity loss, with higher scores indicating greater impairment.

All 6 questions from the WPAI:GH will be utilized for this cohort.

7.6.7. Safety Assessments

Safety assessments conducted during this study include collection of AEs, vital sign measurements, symptom-directed physical examinations, clinical laboratory assessments, Eastern Cooperative Oncology Group (ECOG) performance status, and use of concomitant medications. ECGs will be taken at baseline (Screening) and as clinically indicated throughout the study (see Table 5).

Blood pressure and heart rate should be monitored weekly for the first 8 weeks for those participants receiving niraparib as neoadjuvant therapy and for all participants receiving niraparib as maintenance treatment as outlined in Table 5. In between the on-site visits, a home monitoring device will be provided to participants who will need to record values at home.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood samples and measurement of vital signs and weight. See master protocol for details.

All AEs and serious adverse events (SAEs), regardless of causality, will be collected and recorded for each participant from the day the Prescreening ICF is signed until 30 days after the last dose of study treatment. Any pregnancies that occur are to be reported. All AEs and SAEs experienced by a participant, 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 participant is lost to follow-up or withdraws consent, or until the participant has died. The AESIs for this study are MDS, AML, and secondary cancer (new malignancies other than MDS or AML). AESIs will be collected throughout the study participation and must be reported to the Sponsor as soon as the Investigator becomes aware of them or within 24 hours.

7.6.8. Surgical and Postsurgical Outcomes

The key surgical outcome will be based [redacted]

Other surgical and postsurgical outcomes will be determined based on the collection of peri-operative and postoperative data prior to C4D1 on operation time, estimated blood loss, blood transfusions (i.e., red blood cells, platelets, whole blood, and albumin), hospitalization

length of stay, re-admission for complications, intensive care unit (ICU) stay, infection and other Grade 3 or Grade 4 AEs, and additional procedures.

7.6.9. Healthcare Resource Utilization Questionnaire

A healthcare resource utilization (HCRU) questionnaire will be filled out for all participants randomized to study treatment and may be used to conduct exploratory economic analyses. HCRU includes non-protocol healthcare encounters and associated data, such as provider visits, emergency room visits, hospitalizations (including ward, admission and discharge dates, and primary discharge diagnosis), medications, tests, and procedures.

7.6.10. Tumor Tissue and Blood Sampling

All participants must provide 2 formalin-fixed paraffin-embedded tissue blocks (or slides if blocks are not available) with sufficient tumor content (as confirmed by the Sponsor's designated central and/or testing laboratory) for central HRD testing at Prescreening and exploratory biomarker testing at Prescreening or Screening. If sufficient tumor tissue is provided at Prescreening, participants do not need to provide additional tissue at Screening. CCI [redacted] For participants in Arm 2 only, IDS tumor tissue will also be used for pharmacokinetic (PK) analysis (niraparib concentration).

CCI [redacted] Blood samples will be collected at Prescreening, C1D1, pre-IDS, C4D1, M1D1 and every 3 months thereafter, the EOT Visit, and the Safety Follow-up Visit (Table 5).

Blood samples will be used to evaluate serum-based tumor markers (including CA-125) and other (potential) biomarkers.

Blood samples used to determine the plasma concentrations of niraparib and carboplatin-paclitaxel will be drawn at the following time points:

- For participants randomized to carboplatin-paclitaxel (Arm 1): predose C1D1 only
- For participants randomized to niraparib (Arm 2): predose and 3-hour postdose (± 15 minutes) at C1D1, C2D1, and C3D1 and at the time of IDS (can be done at the pre-IDS assessment)

Details on tumor tissue and blood sample requirements, collection, processing, and management can be found in the Study Laboratory Manual. Any remaining blood and tumor tissue samples may be stored for up to 15 years for future biospecimen research, which may include biomarker testing.

7.6.11. Genetic Sample

A blood sample for DNA isolation will be collected on C1D1 from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Those who do not wish to participate in the genetic research may still participate in the study. Participants may withdraw their consent and have their specimens and all derivates destroyed.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent. Information on the use/analysis of DNA from the genetic sample is provided in Appendix A.

Details on blood sample requirements, collection, processing, and management can be found in the Study Laboratory Manual.

Table 5: Schedule of Events

Procedure	Pre-screening	Screening	Neoadjuvant					Pre-IDS evaluation	IDS[a]	Adjuvant			Maintenance	EOT	Safety Follow-up	Long-term Follow-up
Cycle and Day	**Up to -42d**	**Up to -7d**	**C1D1[b] (±3d)**	**C1D8 (±1d)**	**C1D15 (±1d)**	**C2D1[b] (±3d)**	**C3D1[b] (±3d)**	**≤2 wks prior to IDS**	**Within 3-6 wks post C3D1**	**C4D1 ≤6 wks after IDS**	**C5D1 (±3d)**	**C6D1[c] (±3d) optional**	**M(n)D1 6-9 wks after C5D1 (or C6D1)[d] (±3d)**	**≤7d of last dose**	**≤30d (±7d) after last dose**	**Every 90d (±14d)**
Informed consent	X pre-screening ICF	X														
Inclusion and exclusion criteria review		X[e]														
Demography		X														
Medical, surgical, and cancer history, run-in chemo information		X														
Height		X														
Weight, temperature		X	X			X	X	X	X	X	X	X	X	X	X	
Blood pressure and pulse rate[f]		X	X	X	X	X	X	X		X	X	X	X	X	X	
Symptom-directed PE		X	X	X	X	X	X	X		X	X	X	X	X	X	

Procedure	Pre-screening	Screening	Neoadjuvant					Pre-IDS evaluation	IDS[a]	Adjuvant			Maintenance	EOT	Safety Follow-up	Long-term Follow-up
Cycle and Day	**Up to -42d**	**Up to -7d**	**C1D1[b] (±3d)**	**C1D8 (±1d)**	**C1D15 (±1d)**	**C2D1[b] (±3d)**	**C3D1[b] (±3d)**	**≤2 wks prior to IDS**	**Within 3-6 wks post C3D1**	**C4D1 ≤6 wks after IDS**	**C5D1 (±3d)**	**C6D1[c] (±3d) optional**	**M(n)D1 6-9 wks after C5D1 (or C6D1)[d] (±3d)**	**≤7d of last dose**	**≤30d (±7d) after last dose**	**Every 90d (±14d)**
Peri- and post-operative surgical data[g]									X							
ECOG performance status	X	X	X			X	X	X		X	X	X	X	X	X	
PRO-CTCAE, WPAI:GH[h]			X	X	X	X[h]	X[h]							X		
FACT-GP5[h]			X	X	X	X[h]	X[h]	X					X[h]	X		
EORTC IL136, EORTC IL137[h]			X			X	X	X					X[h]	X		
Tumor tissue samples	X	X[i]							X[j]							
RECIST v1.1 assessment (chest, abdomen, pelvis, and suspected areas) CT or MRI		X[k]						X[k]					X[l]			

Procedure	Pre-screening	Screening	Neoadjuvant					Pre-IDS evaluation	IDS[a]	Adjuvant			Maintenance	EOT	Safety Follow-up	Long-term Follow-up
Cycle and Day	**Up to -42d**	**Up to -7d**	**C1D1[b] (±3d)**	**C1D8 (±1d)**	**C1D15 (±1d)**	**C2D1[b] (±3d)**	**C3D1[b] (±3d)**	**≤2 wks prior to IDS**	**Within 3-6 wks post C3D1**	**C4D1 ≤6 wks after IDS**	**C5D1 (±3d)**	**C6D1[c] (±3d) optional**	**M(n)D1 6-9 wks after C5D1 (or C6D1)[d] (±3d)**	**≤7d of last dose**	**≤30d (±7d) after last dose**	**Every 90d (±14d)**
Laboratory assessments																
Pregnancy test (WOCBP only): serum or urine [u]		X		X	X	X	X	X		X	X	X	X		X	
Serum-based tumor markers (e.g., CA-125)		X	X			X	X	X		X	X	X	X			
CBC with differential	X[m]		X	X	X	X	X	X		X	X	X	X		X	
Coagulation		X														
Blood chemistry		X	X			X	X	X		X	X	X	X		X	
PK/pharmaco-dynamic samples[n]			X			X	X		X[o]							
CCI [redacted]	X[p]		X[q]					X		X[q]			X[r]	X	X	

Procedure	Pre-screening	Screening	Neoadjuvant					Pre-IDS evaluation	IDS[a]	Adjuvant			Maintenance	EOT	Safety Follow-up	Long-term Follow-up
Cycle and Day	**Up to -42d**	**Up to -7d**	**C1D1[b] (±3d)**	**C1D8 (±1d)**	**C1D15 (±1d)**	**C2D1[b] (±3d)**	**C3D1[b] (±3d)**	**≤2 wks prior to IDS**	**Within 3-6 wks post C3D1**	**C4D1 ≤6 wks after IDS**	**C5D1 (±3d)**	**C6D1[c] (±3d) optional**	**M(n)D1 6-9 wks after C5D1 (or C6D1)[d] (±3d)**	**≤7d of last dose**	**≤30d (±7d) after last dose**	**Every 90d (±14d)**
Blood sample for sequencing	X[s]															
Genetic sample			X													
Randomization			X													
Platinum/ taxane infusion	X Run-in cycle of carboplatin-paclitaxel		X Arm 1			X Arm 1	X Arm 1			X	X	X				
Optional bevacizumab or bevacizumab biosimilar infusion (for participants deemed high-risk)										X[t]	X[t]	X[t]	X[t]			
Niraparib dispensation			X Arm 2			X Arm 2	X Arm 2						X			
AEs, SAEs, and AESIs [v]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X

Procedure	Pre-screening	Screening	Neoadjuvant					Pre-IDS evaluation	IDS[a]	Adjuvant			Maintenance	EOT	Safety Follow-up	Long-term Follow-up
Cycle and Day	**Up to -42d**	**Up to -7d**	**C1D1[b] (±3d)**	**C1D8 (±1d)**	**C1D15 (±1d)**	**C2D1[b] (±3d)**	**C3D1[b] (±3d)**	**≤2 wks prior to IDS**	**Within 3-6 wks post C3D1**	**C4D1 ≤6 wks after IDS**	**C5D1 (±3d)**	**C6D1[c] (±3d) optional**	**M(n)D1 6-9 wks after C5D1 (or C6D1)[d] (±3d)**	**≤7d of last dose**	**≤30d (±7d) after last dose**	**Every 90d (±14d)**
Concomitant medication [v]	X	X	X			X	X	X		X	X	X	X	X	X	
HCRU questionnaire			X			X	X	X					X	X	X	
Follow-up anticancer therapies and PD per RECIST v1.1															X	X
ECG[w]		X														

Abbreviations: AE=adverse event; AESI=adverse event of special interest; CA-125=cancer antigen 125; CBC=complete blood count; CT=computerized tomography; CxDx=Cycle x Day x; d=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end-of-treatment; FACT-GP5=Functional Assessment of Cancer Therapy-Item GP5; FFPE=formalin-fixed paraffin-embedded; HCRU=healthcare resource utilization; HRD=homologous recombination deficiency; ICF=informed consent form; ICU=intensive care unit; IDS=interval debulking surgery; MRI=magnetic resonance imaging; MxDx=Cycle x Day x of niraparib maintenance treatment period; PD=progression of disease; PE=physical examination; PK=pharmacokinetics; PRO=patient-reported outcome; PRO-CTCAE=Patient Reported Outcomes-Common Terminology Criteria for Adverse Events; EORTC IL136=European Organisation for Research and Treatment of Cancer Item Library 136; EORTC IL137=European Organisation for Research and Treatment of Cancer Item Library 137; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; SOC=standard of care; VTE=venous thromboembolism; wk=week; WOCBP=woman of childbearing potential; WPAI:GH=Work Productivity and Activity Impairment-General Health.

[a] Sufficient time for recovery of hematologic AEs is allowed before IDS. Pre-IDS evaluations must be done taking into consideration the actual date of IDS and be performed up to 2 weeks prior to IDS.

[b] C1D1 is to be performed up to 5 weeks after Day 1 of the run-in cycle of carboplatin-paclitaxel to accommodate resolution of AEs, HRD test result, and screening procedures. CBC and vital signs must be collected and reviewed prior to dosing on Day 1 of each cycle.

[c] Cycle 6 is optional. If a site chooses to administer a third cycle of adjuvant chemotherapy, all participants treated at this study site must be offered the last cycle (C6) of adjuvant chemotherapy, regardless of treatment received during the neoadjuvant treatment period.

[d] The visit frequency is every 3 weeks during the first 13-14 months and every 3 months thereafter.

[e] Some inclusion and exclusion criteria can be checked at the Prescreening stage (ECOG and CBC).

[f] Weekly blood pressure and heart rate for the first 8 weeks for those participants receiving niraparib as neoadjuvant therapy and for all participants receiving niraparib as maintenance treatment. Measurements should be taken prior to dosing on Day 1 of the cycle. In between on-site visits, a home monitoring device will be provided to participants who will need to record values at home. The values will be reviewed by site personnel during the on-site visits. Paper diaries will be provided to participants to record readings and then be transcribed to the EDC.

[g] Surgical data collected include assessment of no visual residual disease, operation time, estimated blood loss, blood transfusions (i.e., red blood cells, platelets, whole blood, and albumin), hospitalization length of stay, re-admission for complications, ICU stay, infection and other Grade 3 or Grade 4 AEs, and additional procedures.

[h] All PROs are to be done prior to any other study procedure. PRO-CTCAE and WPAI:GH are to be completed weekly during neoadjuvant chemotherapy. EORTC IL136 and EORTC IL137 are to be completed at every site visit during the neoadjuvant treatment period and at M1D1 and every 3 cycles for the first 13-14 months and every 3 months thereafter during niraparib maintenance treatment. FACT-GP5 is to be completed weekly during the neoadjuvant treatment period and at M1D1 and every 3 cycles for the first 13-14 months and every 3 months thereafter during niraparib maintenance treatment. PROs that are done weekly will be done at home by the participant on a provisioned device; the remaining PROs will be done at the site.

[i] If tumor tissue with sufficient tumor content (FFPE blocks or FFPE slides if blocks are not available) is not provided at Prescreening for exploratory biomarker testing, additional tumor tissue should be sent at Screening. Specifications on the collection of tumor tissue are provided in the Study Laboratory Manual.

[j] Sufficient IDS tissue sample will be required for all participants to determine CCI and for exploratory biomarker testing. For participants randomized to niraparib neoadjuvant treatment (Arm 2), snap-frozen tumor biopsy tissue will be also collected (see footnote n).

[k] RECIST v.1.1 tumor assessment via CT or MRI scan of the chest, abdomen, pelvis, and clinically indicated areas is required and will be taken after infusion with platinum-taxane therapy, within the 7 days immediately prior to C1D1. This scan will be referred as "baseline scan." IV contrast-enhanced CT is preferred; in case of contraindication to IV CT contrast (iodine-based), non-contrast CT of chest and IV contrast-enhanced MRI (Gadolinium-based) of the abdomen and pelvis is recommended. Another scan is to be taken after C3D21 and during the neoadjuvant treatment period prior to IDS. If there are lesions noted in the chest and/or other clinically indicated areas at Screening, then repeat scans of these areas at each follow-up will be performed; otherwise, only scans of the abdomen and pelvis are required at each follow-up visit.

[l] During the maintenance treatment period, imaging to assess disease status must occur at M1D1 or within 14 days prior to M1D1 and then every 3 months (±7 days) for 1 year after M1D1, followed by every 6 months (±14 days) during the second year, and every year thereafter until PD per RECIST v1.1, start of alternate anticancer therapy, participant discontinuation of the study, withdrawal of consent to study procedures, becoming lost to follow-up, death, or end of the study. Additional unscheduled RECIST v1.1 CT or MRI scans may be performed if the participant has increasing CA-125 values or suspicious symptoms. Participants who discontinue study treatment due to treatment toxicity or intolerability prior to an investigator assessment of PD per RECIST v1.1 will continue radiographic imaging until PD per RECIST v1.1, start of alternate anticancer therapy, participant discontinuation of the study, withdrawal of consent to study procedures, becoming lost to follow-up, death, or end of the study. Following the completion of 3 years of maintenance treatment, participants will be evaluated clinically and with CA-125-triggered imaging every 6 to 12 months or per local practice.

[m] CBC done per SOC prior to the run-in cycle of carboplatin-paclitaxel must be used to determine eligibility. CBC are to be done within 7 days prior to CxD1 to determine ability to participant to receive the next cycle of platinum-taxane doublet chemotherapy or niraparib.
For the niraparib Arm (Arm 2) only: CBC are to be performed weekly for the first 4 weeks in the neoadjuvant treatment period and for the first 4 weeks in the maintenance treatment period (locally or at the site) for safety monitoring. Assessments should be done prior to dosing on dosing days. Subsequently, CBC will be done at each study visit (every 3 weeks) for the next 10 months of the maintenance treatment period, after which blood tests should be performed every 3 months (following visit Schedule). Note: If dose interruption or modification is required at any point on study because of hematologic toxicity (AE), weekly blood draws for CBC will be monitored until the AE resolves. 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. CBC will be done at every visit and as clinically indicated throughout the study.

[n] Niraparib Arm (Arm 2): 3 predose samples at C1D1 (1 each for niraparib concentration, carboplatin, and paclitaxel concentration), one 3-hour postdose sample (± 15 minutes) at C1D1, 1 predose sample and one 3-hour (± 15 minutes) postdose sample each at C2D1 and C3D1, and 1 sample at the time of IDS (can be done at the pre-IDS visit).
Control Arm (Arm 1): 2 predose samples at C1D1 are required (1 each for carboplatin and paclitaxel concentrations). Actual date and time are to be recorded.

[o] In addition to blood samples mentioned in footnote n, niraparib concentration in snap-frozen tumor tissue from the IDS biopsy for pharmacodynamic analysis should be collected in participants randomized to niraparib (Arm 2).

[p] Sample must be collected before the run-in cycle of carboplatin-paclitaxel.

[q] Sample to be collected predose.

[r] To be collected prior to niraparib administration at M1D1 and every 4 cycles (±7 days) after M1D1 during the maintenance treatment when imaging is performed.

[s] Sample must be collected before the run-in cycle of carboplatin-paclitaxel.

[t] Bevacizumab or bevacizumab biosimilar is optional (≤15 months including adjuvant chemotherapy period) for participants deemed high-risk. Monitor by dipstick urine analysis prior to each bevacizumab or bevacizumab biosimilar infusion for the development or worsening of proteinuria with serial urinalyses during bevacizumab therapy. Participants with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Bevacizumab or bevacizumab biosimilar treatment should be withheld for proteinuria greater than or equal to 2 grams per 24 hours and resumed when less than 2 grams per 24 hours. Bevacizumab or bevacizumab biosimilar treatment should be discontinued in participants who develop nephrotic syndrome. Monitor blood pressure every 2 to 3 weeks during bevacizumab or bevacizumab biosimilar treatment. Continue to monitor blood pressure at regular intervals in patients with bevacizumab-induced or bevacizumab-exacerbated hypertension after discontinuation. Bevacizumab or bevacizumab biosimilar treatment should be discontinued for participants who develop gastrointestinal perforation, tracheoesophageal fistula or any Grade 4 fistula, and fistula formation involving any internal organ.

[u] Pregnancy testing for WOCBP only can be done at site/local lab, at home via the home health clinician, or at a local clinic. If a participant becomes a WONCBP (defined in Appendix 1 of the master protocol) during the study (e.g., post-IDS), then pregnancy testing and contraception will not be required.

[v] Discussions can be held at the site or via a phone call to the participant at home (involving home health clinician or a direct phone call to the participant by site staff).

[w] Baseline ECG is required for all participants. ECG monitoring at other visits are as clinically indicated (at the Investigator's discretion), based on the participants' cardiovascular profile.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

The overall list of eligibility criteria for entry into this study is provided in the master protocol. The following are all eligibility criteria for this cohort (Cohort C) and include eligibility criteria from the master protocol as well as cohort-specific eligibility criteria. Participants must meet all criteria in this cohort-specific supplement in order to be eligible for enrollment in this cohort.

8.1. Inclusion Criteria

Participants will be eligible for entry in this cohort if all of the following criteria for inclusion are met:

Inclusion criteria from the master protocol

C1. Participant must be female ≥18 years of age, able to understand the study procedures, and agree to participate in the study by providing written informed consent.

C2. Participant must have measurable disease according to RECIST v1.1.

C3. Participant has an ECOG performance status of 0 to 2.

C4. Participant has adequate organ function, defined as follows:

a. Absolute neutrophil count ≥1500/µL, without growth factor support (granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor administration is not permitted within 2 weeks of Screening)
b. Platelets ≥100 000/µL without platelet transfusion support within 2 weeks prior to Screening
c. Hemoglobin ≥9 g/dL without transfusion or growth factor (recombinant erythropoietin) within 2 weeks of Screening
d. Serum creatinine ≤1.5× upper limit of normal (ULN) or calculated creatinine clearance ≥50 mL/min using Cockcroft-Gault equation
e. Total bilirubin ≤1.5× ULN, except in participants with Gilbert's syndrome. Participants with Gilbert's syndrome may enroll if direct bilirubin is ≤1.5× ULN.
f. Aspartate aminotransferase and alanine aminotransferase ≤2.5× ULN, unless liver metastases are present, in which case they must be ≤5× ULN
g. International normalized ratio or prothrombin time (PT) ≤1.5× ULN, unless participant is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
h. Activated PTT ≤1.5× ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants. Participants with known lupus anticoagulant and elevated PTT may be eligible on a case-by-case basis after discussion with the Sponsor's Medical Monitor.

C5. Participant is not pregnant or breastfeeding, and at least 1 of the following conditions apply:

– Is not a woman of childbearing potential (WOCBP), as defined in Appendix 1 in the master protocol.

OR

- Is a WOCBP using a contraceptive method that is highly effective (with a failure rate of <1% per year) with low user dependency, as described in Appendix 1 in the master protocol, during the treatment periods and for at least 180 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relation to the first dose of study treatment.
  - A WOCBP must have a negative pregnancy test (highly sensitive urine test or serum test as required by local regulations) within 72 hours before the first dose of study treatment.
    If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
  - Additional requirements for pregnancy testing during and after study treatment are described in Section 11.3.8 of the master protocol.

The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Inclusion criteria specific to this cohort (Cohort C)

C6. Participant has newly diagnosed Stage III or IV ovarian, fallopian tube, or primary peritoneal cancer according to the International Federation of Gynecology and Obstetrics staging criteria.

C7. Participants must provide sufficient tumor tissue at Prescreening and agree to undergo a central HRD tumor testing using a fully validated assay. The participants must be HRd as per central HRD tumor testing result for eligibility.

a. Participants with a documented germline *BRCA*1/2 deleterious or suspected deleterious mutations by Sponsor's permitted test CCI may be allowed to enroll prior to receiving the central test results, provided all inclusion criteria are met. However, tumor sample submitted by these participants will still be required for central HRD confirmation. The list of Sponsor's permitted tests will be provided by the Sponsor.
b. All participants must agree to provide tumor tissue collected from IDS.
c. Participant must provide 2 formalin-fixed paraffin-embedded tissue blocks (or slides if blocks are not available) with sufficient tumor content (as confirmed by the Sponsor's designated central and/or testing laboratory) for central HRD testing at Prescreening and for exploratory biomarker testing at Prescreening or Screening. If sufficient tumor tissue is provided at Prescreening, participants do not need to provide additional tissue at Screening.

C8. Participant must have completed 1 run-in cycle of carboplatin-paclitaxel and not experienced disease progression after this treatment. Completion is defined as receiving ≥50% of the prescribed dose of therapy within 5 weeks.

C9. Participant must not have known contraindication or uncontrolled hypersensitivity to carboplatin and paclitaxel and their excipients and no known pre-existing conditions that would preclude treatment with these agents.

C10. Participant must not have known contraindication or uncontrolled hypersensitivity to niraparib and its excipients.

C11. Participant must not have symptomatic ascites or pleural effusions as defined by the following criterion: presence of fluid in the abdominal or pleural cavities requiring removal within 1 week prior to signing the informed consent.

C12. Participant must agree to complete PRO and work productivity questionnaires throughout the study.

8.2. Exclusion Criteria

Participants will not be eligible for entry in this cohort if any of the criteria for exclusion in the master protocol or in this cohort-specific supplement are met:

Exclusion criteria from the master protocol

C1. Participant has not recovered (i.e., to Grade ≤1 or to Baseline) from prior chemotherapy-induced AEs. Note: Participant with Grade ≤2 neuropathy or alopecia is an exception to this criterion and may qualify for the study.

C2. Participant has a known diagnosis of immunodeficiency or is receiving systemic steroid therapy exceeding an equivalent of prednisone 10 mg daily or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.

C3. Participant is currently participating in a treatment study or has participated in a study of an investigational agent within 4 weeks of the first dose of treatment.

C4. Participant has received prior systemic anticancer therapy including cytotoxic chemotherapy, PARP inhibitor, immune checkpoint inhibitors, hormonal therapy given with the intention to treat cancer, or biological therapy within 3 weeks of the first dose of study treatment. This washout period is required to ensure prior therapy is not confounding the toxicity profile of the investigational study drug or study drug combinations in cohorts.
Note: For this cohort (Cohort C), this criterion will not apply because the population will include only participants who are eligible for neoadjuvant chemotherapy.

C5. Participant has received live vaccine within 14 days of planned start of study therapy.

C6. Participant has symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled", central nervous system [CNS] disease must have undergone treatment [e.g., radiation or chemotherapy] at least 1 month prior to study entry. The participant must not have any new or progressive signs or symptoms related to the CNS disease and must be taking ≤10 mg of prednisone or equivalent per day or no steroids.) Participant who has untreated brain metastases and who is not symptomatic may enroll if the Investigator feels that the treatment of these metastases is not indicated. A scan to confirm the absence of brain metastases is not required. Participant with spinal cord

compression may be considered if she has received definitive treatment for this and evidence of clinically SD for 28 days prior to the first dose of study treatment.

C7. Participant had major surgery within 4 weeks of starting the study or participant has not recovered from any effects of any major surgery.

C8. Participant has a known additional malignancy that progressed or required active treatment within the last 2 years because reoccurrence of another malignancy would confound interpretation of ORR by RECIST v1.1 criteria. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cancer that is considered to be low risk for progression by the Investigator.

C9. Participant is considered to be in poor medical condition or at high medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. These include, but are not limited to, coronavirus disease 2019, significant cardiovascular disease (e.g., significant cardiac conduction abnormalities, myocardial infarction, cardiac arrhythmia or unstable angina within 6 months prior to enrollment, New York Heart Association Grade ≥2 congestive heart failure, uncontrolled hypertension, serious cardiac arrhythmia requiring medication, Grade ≥2 peripheral vascular disease, and history of cerebrovascular accident within 6 months prior to enrollment), uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, and any psychiatric disorder that prohibits obtaining informed consent.

C10. Participant has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, might interfere with the participant's participation for the full duration of the study treatment, or is not in the best interest of the participant to participate.

C11. Participant has known active hepatitis B (e.g., hepatitis B surface antigen reactive) or hepatitis C (e.g., hepatitis C virus ribonucleic acid [qualitative] is detected).

Exclusion criteria specific to this cohort (Cohort C)

C12. Participant has low-grade or Grade 1 epithelial OC or mucinous, germ cell, transitional cell, carcinosarcoma, or undifferentiated tumor.

C13. Participant has contraindications to surgery.

C14. Participant has a bowel obstruction by clinical symptoms or CT scan, subocclusive mesenteric disease, abdominal or gastrointestinal fistula, gastrointestinal perforation, or intra-abdominal abscess.

C15. Participant has any known history or current diagnosis of MDS or AML.

C16. Participant is at increased bleeding risk due to concurrent conditions (e.g., major injuries or major surgery within the past 28 days prior to the start of study treatment and/or history of hemorrhagic stroke, transient ischemic attack, subarachnoid hemorrhage, or clinically significant hemorrhage within the past 3 months).

C17. Participant is immunocompromised. Participants with splenectomy are allowed. Participants with known HIV are allowed if they meet all of the following criteria:

a. Cluster of differentiation 4-positive T cell count ≥350/µL and viral load <400 copies/mL
b. No history of AIDS-defining opportunistic infections within 12 months prior to enrollment
c. No history of HIV-associated malignancy for the past 5 years
d. Concurrent antiretroviral therapy as per the most current National Institutes of Health Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV started >4 weeks prior to study enrollment

C18. Participant received prior treatment for high-grade non-mucinous epithelial ovarian, fallopian tube, or peritoneal cancer (e.g., prior surgery, immunotherapy, anticancer therapy [with the exception of 1 run-in cycle of carboplatin-paclitaxel], or radiation therapy).

C19. Participant has an active autoimmune disease that has required systemic treatment in the past 2 years. Replacement therapy is not considered a form of systemic therapy (e.g., thyroid hormone or insulin).

C20. Participant is unable to swallow orally administered medication or has a gastrointestinal disorder likely to interfere with absorption of the study medication.

C21. Participant received whole blood transfusions in the 2 weeks prior to entry to the study (packed red blood cells and platelet transfusions are acceptable outside of 2 weeks prior to treatment).

8.3. Withdrawal Criteria

8.3.1. Discontinuation from Treatment

Examples of reasons for discontinuing study treatment applicable across cohorts are presented in the master protocol. Details of required dose modifications related to toxicity, including interruptions, reductions, and permanent discontinuations, are provided in Section 7.4.1.

Discontinuation of study treatment does not affect a participant's participation in the study. The participant should comply with the protocol Schedule of Events (Table 5) and data collection should continue (e.g., safety). The participant must be followed for survival, up to the end of the study as defined in Section 7.1.6.

If the participant considers study withdrawal at the time of study treatment discontinuation, modified follow-up options should be discussed, if appropriate (see Section 8.3.2).

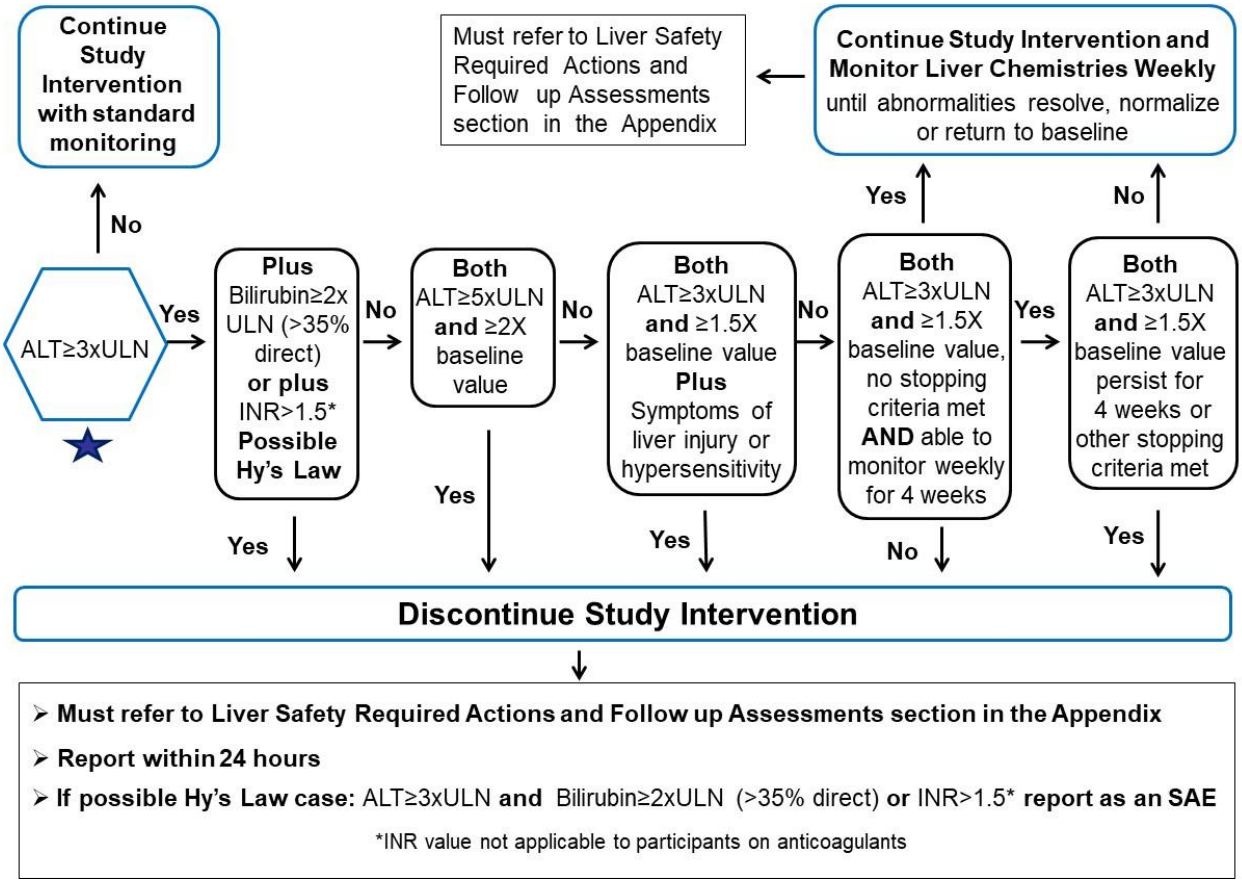
8.3.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in Figure 3 or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the Investigator believes that it is in the best interest of the participant

Figure 3: Cohort C Liver Stopping and Monitoring Event Algorithm



Abbreviations: ALT=alanine aminotransferase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal.

Refer to Appendix B for required liver safety actions and follow-up assessments and for required process for study intervention restart/rechallenge if considered for the participant.

8.3.1.2. Study Intervention Restart or Rechallenge After Liver Stopping Criteria Met

Study intervention restart/rechallenge after liver chemistry stopping criteria are met is allowed in Cohort C of this study. If participant meets liver chemistry stopping criteria, do not restart/rechallenge participant with study intervention unless all of the following occur:

- GSK Medical Governance approval **is granted**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for intervention restart/rechallenge is signed by the participant and participant is informed of any associated risks

Refer to Appendix B Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Restart/Rechallenge Guidelines for details on restart/rechallenge process.

If GSK Medical Governance approval to restart/rechallenge the participant with study intervention **is not granted**, then the participant must permanently discontinue study intervention and should continue in the study for protocol-specified follow-up assessments.

8.3.2. Discontinuation from the Study

Guidance on discontinuation of participants from the study is provided in the master protocol.

All participants must be followed for survival, up to the end of the study as defined in Section 7.1.6 and Section 8.3.1.

For participants considering withdrawal from study, a modified follow-up option should be discussed if appropriate, to allow reduced collection of data such as vital status (at minimum) and subsequent anticancer therapy. When appropriate, this can be done via a telephone contact with the participant, a contact with others e.g., a relative or treating physician, or collecting information from medical records. The agreed approach should be recorded in the medical records. A participant who agrees to modified follow-up is not considered to have withdrawn from the study.

Site personnel, or a trusted independent third party, will attempt to collect the vital status information for all randomized participants who discontinued from the study due to consent withdrawal or loss-to-follow-up, including those who did not receive study intervention, within legal and ethical boundaries. Public sources may be searched for vital status information. If the vital status of a participant is determined as known alive or deceased, this will be documented along with other relevant study information. Sponsor personnel will not be involved in any attempts to collect vital status information.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. Use of vital status information obtained from independent third party or review of public sources (public records or other allowable routes) for those participants withdrawn or lost-to-follow-up is permitted, dependent upon local regulations.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Study Drug

The study drugs for this cohort are described in Table 6. The investigational product is niraparib, carboplatin-paclitaxel (or alternative platinum-taxane doublet chemotherapy as relevant) is the reference therapy.

Table 6: Study Drugs

	Investigational Product	**Reference Therapy**		
Product name	Niraparib	Carboplatin	Paclitaxel	Bevacizumab or bevacizumab biosimilar (optional)
Type	Drug	Drug	Drug	Drug
Dosage form (formulation)	CCI	Solution for Infusion (vial)	Solution for Infusion (vial)	Solution for Infusion (vial)
Unit dose	CCI			
Dose Level	See Section 10.5.1	See Section 10.5.2	See Section 10.5.2	See Section 10.5.3
Route of administration	Oral	IV	IV	IV
Physical description (Packaging and Labeling; also see Section 10.2)	CCI in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement.	Solution for IV infusion Each package/vial will be labeled as required per country requirement.	Solution for IV infusion Each package/vial will be labeled as required per country requirement.	Solution for IV infusion Each package/vial will be labeled as required per country requirement.
Use	Experimental	Active comparator (SOC)	Active comparator (SOC)	SOC
IMP and NIMP/AxMP	IMP	IMP	IMP	AxMP/NIMP
Sourcing	Provided centrally by the Sponsor	Provided locally by the study site (or centrally if required)	Provided locally by the study site (or centrally if required)	Provided locally by the study site

Abbreviations: AUC=area under the concentration versus time curve; AxMP=auxiliary medicinal product; IMP=investigational medicinal product; IV=intravenous; NIMP=non-investigational medicinal product; SOC=standard of care; QxW=every x weeks.

9.2. Concomitant Medications

Details on the definition and recording of concomitant medications are provided in the master protocol.

9.2.1. Prohibited Medications

Known prior medications that exclude a patient from participating in this cohort are described in the exclusion criteria (see Section 8.2).

Participants are prohibited from receiving the following therapies during the Screening and treatment periods of this study:

- Systemic anticancer or biological therapy
- Immunotherapy (except study treatment specified in the relevant cohort-specific supplement)
- Chemotherapy (except study treatment specified in the relevant cohort-specific supplement)
- Hormonal therapy given with the intention to treat the primary cancer
- Radiation therapy is prohibited within 3 weeks prior to Day 1 and during study treatment. Note: Palliative radiation therapy to a small field while on study should be discussed with the Sponsor's Medical Monitor on a case-by-case basis.
- Any surgery not prespecified in the cohort-specific Schedule of Events that involves tumor lesions; however, specific situations should be discussed on a case-by-case basis with the Sponsor's Medical Monitor. Paracentesis while the participant is on study will be permitted after discussion with the Sponsor. Note: Administration of radiation therapy or surgery done that involves tumor lesions will be considered as disease progression at the time the procedure is performed.
- Live vaccines within 14 days prior to the first dose of study treatment. Seasonal flu vaccines that do not contain live viruses are allowed. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus CalmetteGuérin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. The use of live COVID-19 adenoviral vaccines within 14 days prior to the first dose of treatment or while participating in the study must be discussed with the Sponsor's Medical Monitor. Intranasal influenza vaccines (e.g., FluMist) are live attenuated vaccines and are not allowed.
- Investigational agents other than niraparib
- Prophylactic cytokines (i.e., granulocyte colony-stimulating factor) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current American Society of Clinical Oncology guidelines

The niraparib safety profile includes risk for thrombocytopenia and bevacizumab may increase the potential for bleeding (hemorrhage); therefore, participants should be advised to use caution when taking anticoagulants (e.g., warfarin) and antiplatelet drugs (e.g., aspirin).

Caution is recommended when niraparib is combined with active substances with cytochrome P450 enzyme (CYP)3A4-dependent metabolism and, notably, those having a narrow therapeutic range (e.g., cyclosporine, tacrolimus, alfentanil, ergotamine, pimozide, quetiapine, and halofantrine).

Caution is recommended when niraparib is combined with active substances with CYP1A2-dependent metabolism and, notably, those having a narrow therapeutic range (e.g., clapzine, theophylline, and ropinirole). Caution is then recommended when niraparib is combined with substrates of breast cancer resistance protein (e.g., irinotecan, rosuvastatin, simvastatin, atorvastatin, and methotrexate).

Niraparib is an inhibitor of multidrug and toxin extrusion transporter 1 and 2 with a half-maximal inhibitory concentration of 0.18 µM and ≤0.14 µM, respectively. Increased plasma concentrations of co-administered medicinal products that are substrates of these transporters (e.g., metformin) cannot be excluded.

Caution is recommended when niraparib is combined with active substances that undergo an uptake transport by organic cation transporter 1 (e.g., metformin).

Physicians should follow the prescribing information for Zejula, carboplatin, paclitaxel, and bevacizumab or bevacizumab biosimilar, and the niraparib IB for information on the general recommendation and management of the participants receiving these therapies.

9.2.2. Contraception

Contraception guidelines are provided in the master protocol.

If a participant becomes a WONCBP (defined in Appendix 1 of the master protocol) during the study (e.g., post-IDS), then pregnancy testing and contraception will not be required.

9.2.3. Rescue Medications and Supportive Care Guidelines

Supportive care measures for AEs during treatment with niraparib should be provided as deemed necessary by the treating Investigator according to local institutional practice and/or guidance in the appropriate prescribing information.

9.2.4. Other Study Restrictions

Other study restrictions are provided in the master protocol.

9.3. Treatment Compliance

Overall study treatment compliance information is presented in the master protocol. Study treatment will be administered by investigational site personnel at investigational sites as detailed in Section 10.5.

9.4. Randomization and Blinding

All participants will be centrally randomized using an Interactive Voice/Web Response System. Before the study is initiated, the telephone number and call-in directions for the Interactive Voice Response System and/or the log in information and directions for the Interactive Web Response

System will be provided to each site. Randomization will be stratified by *BRCA* mutational status (*BRCAmut* vs B*RCAwt*/unknown).

This study is open-label.

To mitigate the risk of introducing bias in the assessment of treatment effect, various treatment-sensitive clinical data types are required to remain blinded to specified roles on the central study team until Database Freeze. No data aggregation (efficacy, safety, or PK) by treatment arm is to be performed, except for prespecified interim analyses. Details of blinding/masking treatment-sensitive data are included in the study-level treatment-sensitive data plan, which describes how these data will be managed. This study will be monitored by a GSK Data Review Committee that is independent of the GSK study team who are directly involved in this trial.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

10.1.1. Niraparib

Niraparib ([3S]-3-[4-[7-(aminocarbonyl)-2H-indazol-2-yl] phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly-selective PARP1 and PARP2 inhibitor. The excipients for niraparib are lactose monohydrate and magnesium stearate.

10.1.2. Carboplatin and Paclitaxel

Carboplatin (platinum, diamine [1,1-cyclobutanedicarboxylato(2-)-*O,O'*]-,[*SP*-4-2]) is a platinum coordination compound. The main target of carboplatin is DNA. Carboplatin for infusion is supplied as a sterile, pyrogen-free, aqueous solution for infusion.

Paclitaxel (5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine) is a natural product with antitumor activity, derived from *Taxus baccata*. Paclitaxel for infusion is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution prior to intravenous infusion.

Additional information on carboplatin and paclitaxel can be found in the prescribing information for each agent as well as in the Study Reference Manual.

10.1.3. Optional Bevacizumab or Bevacizumab Biosimilar

Bevacizumab or bevacizumab biosimilar is an antiangiogenic recombinant humanized immunoglobulin G1 monoclonal antibody against the vascular endothelial growth factor. Bevacizumab for infusion is a clear to slightly opalescent, colorless to pale brown, sterile solution.

Additional information on bevacizumab or bevacizumab biosimilar can be found in the prescribing information as well as in the Study Reference Manual.

10.2. Study Drug Packaging and Labeling

Overall, niraparib packaging and labeling is described in the master protocol, Study Reference Manual, and IB. Carboplatin, paclitaxel, and bevacizumab are described in their respective prescribing information as per the local label.

10.3. Study Drug Storage

Study treatment storage is described in the master protocol.

10.4. Study Drug Preparation

The Study Reference Manual contains specific instructions for the preparation of each dose of the niraparib CCI [redacted] Refer to local prescribing information for instructions for the preparation of platinum-taxane doublet chemotherapy and bevacizumab.

10.5. Administration

10.5.1. Niraparib

Niraparib will be supplied as CCI [redacted]. Participants will be instructed to take their niraparib dose once a day continuously throughout each cycle or as instructed by the Investigator. Niraparib will be dispensed to participants at each scheduled visit.

Participants will be instructed to take niraparib at the same time each day. Bedtime administration may be a potential method for managing nausea. Participants must swallow and not chew all CCI [redacted] The consumption of water and food with CCI [redacted] is permissible. If a participant vomits or misses a dose of niraparib, a replacement dose should not be taken.

For participants randomized to niraparib neoadjuvant treatment, the starting dose will be as follows:

- 200 mg CCI [redacted] for participants with an actual body weight <77 kg OR screening platelet count <150 000/µL on C1D1
- 300 mg (CCI [redacted]) for participants with an actual body weight ≥77 kg AND screening platelet count ≥150 000/µL on C1D1

Niraparib will be administered orally once daily continuously throughout each of the three 21-day cycles.

For participants receiving niraparib maintenance treatment, independent of the treatment they received during the neoadjuvant treatment period, the starting dose will be as follows:

- 200 mg CCI [redacted]) for participants with an actual body weight <77 kg OR platelet count <150 000/µL on M1D1
- 300 mg (CCI [redacted]) for participants with an actual body weight ≥77 kg AND platelet count ≥150 000/µL on M1D1
- For participants who received niraparib in the neoadjuvant period and experienced niraparib dose reductions due to AEs, the Investigator, in consultation with the Sponsor's Medical Monitor, will determine the safest starting dose in the maintenance setting

Niraparib will be taken once daily continuously throughout each 21-day cycle.

Dose modifications, if any, will be based on treatment side effects (Section 7.4.1.1), not upon changes in the participant's actual body weight during study participation.

The Study Reference Manual contains descriptions of the packaging of niraparib and instructions for the preparation and administration of niraparib. Niraparib can be shipped direct-to-patient from the investigational site to the participant's home address, details are provided in the master protocol and the Study Reference Manual.

10.5.2. Carboplatin and Paclitaxel

Carboplatin will be infused intravenously over 60 minutes at the prescribed dose of area under the concentration versus time curve of 5 to 6 mg/mL•min on Day 1 of every 21-day cycle. The carboplatin dose will be determined by the Investigator, taking into consideration the

participant's pre-existing medical conditions and the recommendations provided in the prescribing information.

Paclitaxel will be administered in a similar fashion over 180 minutes at the prescribed dose of 175 mg/m^2 on Day 1 of every 21-day cycle. All participants should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists as indicated in the prescribing information. Paclitaxel is recommended to be administered before carboplatin, however, carboplatin may be administered first, if this is the current local institutional practice.

Prior to each chemotherapy administration, all of the following criteria must be met: 1) absolute neutrophil count ≥1500/µL or ≥1000/µL if granulocyte colony-stimulating factor is to be administered, 2) platelet count ≥100 000/µL, 3) hemoglobin ≥9 g/dL.

If a participant experiences a hypersensitivity to carboplatin, then cisplatin may be used in place of carboplatin. Desensitization to carboplatin will not be allowed on the study. If a participant experiences hypersensitivity or clinically significant neuropathy on paclitaxel treatment, docetaxel can be substituted per the Investigator's discretion.

Carboplatin (or cisplatin) and paclitaxel (or docetaxel) must be given on the same day; hence, delays in 1 study treatment should result in delay of all study treatments until they can all safely be given.

10.5.3. Optional Bevacizumab or Bevacizumab Biosimilar

The initial dose of optional bevacizumab or bevacizumab biosimilar will be infused intravenously over 90 (±15) minutes at the prescribed dose of 7.5 mg/kg or 15 mg/kg on Day 1 of every 21-day cycle. If the first infusion is tolerated without infusion-associated AEs (fever and/or chills), the second infusion may be delivered over 60 (±10) minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. Sites can defer to local practice for administration if different from the process described here and if bevacizumab or bevacizumab biosimilar should be given before or after carboplatin-paclitaxel.

Prior to administering bevacizumab or bevacizumab biosimilar, monitor by dipstick urine analysis for the development or worsening of proteinuria. Participants with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection.

10.6. Study Drug Accountability

Study treatment accountability is described in the master protocol.

10.7. Study Drug Handling and Disposal

Study treatment handling and disposal are described in the master protocol and the cohort-specific Study Reference Manual.

11. ASSESSMENT OF EFFICACY

11.1. Primary Efficacy Endpoint

The primary efficacy endpoint for this cohort is pre-IDS unconfirmed ORR, defined as the percentage of participants with unconfirmed CR or PR on study treatment pre-IDS as assessed per RECIST v1.1 by the Investigator.

A description of evaluation of tumor response by RECIST v1.1. is provided in the master protocol.

11.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints for this cohort are as follows:

- Incidence of CA-125 progression per GCIG CA-125 response criteria
- PFS, defined as the time from the date of treatment randomization to the date of first documentation of PD per RECIST v1.1 or death by any cause, whichever occurs first, as determined by the Investigator
- OS, defined as the time from the date of treatment randomization to the date of death by any cause
- TFST, defined as the time from the date of treatment randomization to the date of first subsequent anticancer therapy or death

11.3. Patient-reported Outcome Endpoints

Secondary PRO endpoints, arranged in order of clinical importance, are as follows:

- To determine overall tolerability toward treatment: change over time in frequency and severity of the items on the PRO-CTCAE during neoadjuvant treatment
- To determine symptom tolerability: change from baseline in FACT-GP5 during neoadjuvant treatment
- To determine overall health status: change from baseline in EORTC QLQ-C30 items (EORTC IL136) pre-IDS
- To determine OC-specific HRQoL and symptoms: change from baseline in EORTC QLQ-OV28 gastrointestinal items (EORTC IL137) pre-IDS

Exploratory PRO endpoints, arranged in order of clinical importance, are as follows:

- To determine overall health status: change from baseline in EORTC QLQ-C30 items (EORTC IL136) during the niraparib maintenance treatment period
- To determine OC-specific HRQoL and symptoms: change from baseline in EORTC QLQ-OV28 items (EORTC IL137) during the niraparib maintenance treatment period
- To determine work productivity: change from baseline in WPAI:GH during neoadjuvant treatment period

11.4. Exploratory Endpoints

Exploratory Efficacy Endpoints include the following:

CCI [redacted]

11.4.1.1. Surgical and Postsurgical Outcomes

The key exploratory endpoint to evaluate surgical outcome is the CCI [redacted] by the gynecologic/surgical oncologist.

Additional exploratory endpoints to evaluate other surgical and postsurgical outcomes are as follows:

CCI [redacted]

11.4.1.2. Healthcare Resource Utilization

Medical resource utilization and health economics will be collected using a HCRU questionnaire and results may be compared between participants who receive neoadjuvant niraparib and participants who received neoadjuvant platinum-taxane doublet chemotherapy.

11.4.1.3. Pathological Complete Response

CCI [redacted]

CCI [redacted]

11.4.1.4. Biomarker Endpoints

Tumor tissue and/or blood samples may be assessed to identify potential disease- or treatment-related biomarkers that would associate with tumor responses to treatment. Additionally, samples may be assessed to evaluate the evolution of the molecular profile of the tumor and tumor microenvironment in response to treatment.

11.4.1.5. Pharmacokinetic and Pharmacodynamic Endpoints

The PK endpoints are as follows:

- Residual plasma concentrations of carboplatin and paclitaxel at C1D1
- Niraparib concentration throughout the neoadjuvant treatment period
- Niraparib concentration in tumor tissue from IDS biopsy

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety parameters for this study are described in the master protocol.

Safety endpoints include frequency and severity of treatment-emergent AEs, SAEs, AEs of special interest, and dose modification (i.e., interruptions and discontinuations).

12.2. Adverse Events and Special Situations

The severity of AEs will be graded according to CTCAE v5.0. Guidance on AEs and special situations is provided in the master protocol.

13. STATISTICS

An overall description of the statistics for this study is provided in the master protocol. Additional details are provided in the statistical analysis plan (SAP).

All analyses will include summary statistics, including the number and percentage for categorical variables and the number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using the Kaplan-Meier method.

13.1. Sample Size Determination

Sample size calculation was performed using CCI

CCI [redacted]

Randomization will be stratified based on *BRCA* mutational status (Section 9.4).

13.2. Planned Analyses

CCI [redacted]

13.2.1. Analysis Populations

- ITT Population: All randomized participants whether or not randomized treatment was administered.
- Safety Population: All randomized participants who receive at least one dose of study treatment.
- PK Population: All participants in the safety analysis set from whom at least one postdose PK sample has been obtained and analyzed.

Additional analysis populations may be defined in the SAP.

13.2.2. Efficacy Analyses

All efficacy analyses will include summary statistics as described in the master protocol.

13.2.2.1. Primary Efficacy Analysis

The primary endpoint of pre-IDS ORR will be analyzed in the ITT Population. The pre-IDS ORR difference will be evaluated between the niraparib and the platinum-taxane doublet

chemotherapy neoadjuvant treatments. The 2-sided 80% CI of the pre-IDS ORR difference will be provided.

13.2.2.2. Secondary Efficacy Analysis

The PFS analysis will be assessed by RECIST v.1.1 criteria based on investigator assessment.

The distribution of PFS, OS, and TFST for each treatment arm will be estimated using the Kaplan-Meier method and will be compared between the 2 treatment arms using log-rank test stratified by the stratification factor used for randomization (i.e., *BRCA* mutational status; Section 9.4). The HR and corresponding 95% CI will be estimated from Cox proportional hazard model stratified by randomization factors with treatment arm as the explanatory variable. The PFS rates at 12, 18, and 24 months will also be estimated from the Kaplan-Meier curve. The censoring rules for the PFS, OS, and TFST analyses will be detailed in the SAP.

The CA-125 progression analysis will be based on GCIG CA-125 response criteria using the following rules:

- Participants with elevated CA-125 pretreatment and a reduction of CA-125 to within the normal range on study must show evidence of CA-125 ≥2× ULN on 2 occasions at least 1 week apart
- Participants with elevated CA-125 pretreatment that never reduces to within the normal range on study must show evidence of CA-125 ≥2× the nadir value on 2 occasions at least 1 week apart
- Participants with CA-125 in the normal range pretreatment must show evidence of CA125 ≥2× ULN on study on 2 occasions at least 1 week apart

Additional details will be provided in the SAP.

13.2.2.3. Exploratory Efficacy Analysis

CCI [redacted] The 2-sided 80% CI of the difference will be provided.

13.2.3. Patient-reported Outcome Analyses

The PRO assessments will be analyzed descriptively by changes from baseline in overall score, sub-scores, and individual items when applicable. A repeated measures model adjusting for covariates may be conducted.

13.2.4. Safety Analyses

Safety will be evaluated in the Safety Analysis Population based on the incidence and severity of treatment-emergent AEs, SAEs, treatment discontinuations or dose delays or reductions due to AEs, AESIs, changes in ECOG performance status, changes in clinical laboratory results (hematology and chemistry), vital sign measurements, observations during symptom-directed physical examination, and use of concomitant medications. All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities coding system.

13.2.4.1. Pharmacokinetic and Pharmacodynamic Analyses

A summary of niraparib plasma concentration measurements will be provided for participants in the PK population. A by-participant listing and summary of the residual carboplatin and paclitaxel plasma concentrations predose at C1D1 will be provided for all randomized participants.

Data from this study may be combined with data from other niraparib studies for population PK analysis. If performed, the analysis will be fully described in stand-alone analysis plans and reported separately from the main clinical study report.

An overview of the niraparib tumor tissue exposure will be provided for all participants randomized to niraparib neoadjuvant treatment (Arm 2).

13.2.4.2. Biomarker Analysis

CCI

[redacted]

13.2.4.3. Additional Exploratory Analyses

Details on additional exploratory analyses will be provided in the SAP.

13.2.5. Interim Analysis

CCI

[redacted]

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access to source data and documents is described in the master protocol.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Quality tolerance limits will be pre-defined in the Study Reference Manual to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and deviations from the quality tolerance limits and remedial actions taken will be summarized in the clinical study report.

Additional information on quality control and quality assurance is provided in the master protocol.

16. ETHICS

Ethics is described in the master protocol.

17. DATA HANDLING AND RECORDKEEPING

Data handling and recordkeeping is described in the master protocol.

18. PUBLICATION POLICY

Publication policy is described in the master protocol.

19. LIST OF REFERENCES

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APPENDIX A. GENETICS

Use/analysis of DNA:

- Genetic variation may impact a participant's response to study treatment, susceptibility, severity, and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and Institutional Review Board/Independent Ethics Committee allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to niraparib or ovarian cancer and related diseases. They may also be used to develop tests/assays (including diagnostic tests) related to niraparib (monotherapy or combination therapy, or study treatments of this drug class) and ovarian cancer (or related cancer indications). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to niraparib (monotherapy or combination therapy) or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on niraparib (or study treatments of this class) continues but no longer than 15 years after the last participant's last visit or other period as per local requirements.

APPENDIX B. LIVER SAFETY: REQUIRED ACTIONS AND FOLLOW-UP ASSESSMENTS AND STUDY INTERVENTION RESTART/RECHALLENGE GUIDELINES

Table 7: Liver Chemistry Stopping Criteria and Required Follow-up Assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT Absolute	**Both** ALT ≥5× ULN **and** ≥2× baseline value
ALT Increase	**Both** ALT ≥3× ULN **and** ≥1.5× baseline value that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3× ULN **and** total bilirubin ≥2× ULN (>35% direct bilirubin)
INR[2]	ALT ≥3× ULN **and** INR >1.5
Cannot Monitor	**Both** ALT ≥3× ULN **and** ≥1.5× baseline value that cannot be monitored for 4 weeks
Symptomatic[3]	**Both** ALT ≥3× ULN **and** ≥1.5× baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions, Monitoring, and Follow-up Assessments	
Actions	**Follow-up Assessments**
• **Immediately** discontinue study intervention • Report the event to GSK **within 24 hours** • Complete the liver event eCRF and complete SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow-up assessments as described in the Follow-up Assessments column • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING**) **MONITORING:** **If ALT ≥3× ULN AND total bilirubin ≥2× ULN or INR >1.5:** • Repeat liver chemistries (include ALT, AST, ALP, total bilirubin, and INR) and perform	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend • Blood sample for PK analysis, obtained within 144 hours after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), gamma glutamyl transferase (GGT), glutamate dehydrogenase (GLDH), and serum albumin • Fractionate bilirubin, if total bilirubin ≥2× ULN • Obtain CBC with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury or hypersensitivity on the liver event eCRF • Record use of concomitant medications on the concomitant medications report form, including acetaminophen, herbal remedies,

liver event follow-up assessments within **24 hours** • Monitor participants twice weekly until liver chemistries resolve, stabilize, or return to within baseline • A specialist or hepatology consultation is recommended **For all other criteria (total bilirubin <2× ULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistries resolve, stabilize, or return to within baseline **RESTART/RECHALLENGE** • **Restart/rechallenge is allowed per protocol, but do not resume study intervention unless GSK approval is granted** • If restart/rechallenge is **not granted**, permanently discontinue study intervention and continue participant in the study for any protocol-specified follow-up assessments.	recreational drugs, and other over the counter medications • Record alcohol use on the liver event alcohol intake form **If ALT ≥3× ULN AND total bilirubin ≥2× ULN or INR >1.5**, obtain the following in addition to the assessments listed above: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins) • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week. (e.g., where the participant has been resident in the clinical unit throughout) [James, 2009] • Liver imaging (ultrasound, magnetic resonance, or computerized tomography to evaluate liver disease); complete liver imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In participants when serology raises the possibility of autoimmune hepatitis (AIH) o In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In participants with acute or chronic atypical presentation • If liver biopsy conducted, complete liver biopsy form.

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CBC=complete blood count; DILI=drug-induced liver injury; eCRF=electronic case report form; GSK=GlaxoSmithKline; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalized ratio; PCR=polymerase chain reaction; PK=pharmacokinetics; SAE=serious adverse event; SRM=Study Reference Manual; ULN=upper limit of normal.

[1] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3× ULN and total bilirubin ≥2× ULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

[2] All events of ALT ≥3× ULN and total bilirubin ≥2× ULN (>35% direct bilirubin) or ALT ≥3× ULN and INR >1.5, which may indicate severe liver injury (possible "Hy's Law"), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.

[3] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

[4] Includes Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); and Hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].

[5] Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Table 8: Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3× ULN and ≥1.5× baseline value and not meeting any stopping criteria**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety • Participant can continue study intervention • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin, and INR) until they resolve, stabilize, or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3× ULN and <1.5× baseline value, and bilirubin <2× ULN and INR ≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GSK=GlaxoSmithKline; INR=international normalized ratio; ULN=upper limit of normal.

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