Statistical Analysis Plan

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: 30 Nov 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. On Page 1 of the Cohort C-specific SAP, the master protocol study record NCT ID (NCT03574779) is referenced, as the development of this SAP preceded the availability of the cohort specific NCT ID.

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol 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
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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1.0	28 Mar 2022	Version 1.0 (15-Oct-2021)	Not Applicable	Original version
2.0	17 Jul 2023	Version 1.0 (15-Oct-2021)	Multiple	Multiple analyses clarified and re-reviewed by team
3.0	30 Nov 2023	Version 2.0 (31-Oct-2023)	Section 1.1.1: updated objectives/endpoints table to be consistent with effective protocol, included pre-IDS DCR, pre-maintenance unconfirmed ORR and pre-maintenance DCR as exploratory endpoints. Section 1.2: Study design schematic updated. Section 2: updated analysis timepoints for long-term outcomes. Section 4.1.1: details on actual *BRCA* strata provided for programming derivation purposes. Section 4.2.2: changed primary analysis population to ITT. Section 4.2.2.1: Sensitivity Analysis 3 updated to use Pre-IDS Response Evaluable Analysis Set; Sensitivity Analysis 4 added to the SAP. Section 4.2.3: changed minimum sample size requirement for subgroup analysis from 20 to 10. Clarification added to the footnote. Section 5.5 added to define additional analysis endpoints. Section 5.7.1: section updated to align with other studies in the Niraparib portfolio. Section 5.8.2.2: Table 7 updated. Section 5.8.4: included further outputs requested by the DRC. Section 6: statement regarding additional participant recruitment added in case of drop-out rates. Statement regarding randomization stratification factor added. Section 7.2.2.4 added for clarification of EOS. Section 7.2.6 and Table 11 visit windowing derivations updated. Section 7.5: updated abbreviations.	To align with changes in Master Protocol Amendment 2.0 and Protocol Amendment 1.0 for Cohort C, and address DRC feedback post first safety Interim Analysis.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 213357 (OPAL) Cohort C, the planned analyses to support DRC reviews (as per DRC charter) and some supplementary analyses that may not form part of the CSR.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objective and Endpoints

Objectives	Endpoints
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).	Pre-interval debulking surgery (pre-IDS) unconfirmed Overall Response Rate (ORR), defined as the percentage of participants with unconfirmed complete response (CR) or partial response (PR) on study intervention pre-IDS as assessed per RECIST v1.1 by the Investigator.
Secondary	
To evaluate clinical benefit by Gynecological Cancer InterGroup (GCIG) cancer antigen 125 (CA-125) response criteria.	Incidence of CA-125 progression per GCIG CA-125 response criteria.
To evaluate clinical benefit as measured by progression-free survival (PFS) per RECIST v1.1 by Investigator assessment.	PFS, defined as the time from the date of treatment randomization to the date of first documentation of progression of disease (PD) per RECIST v1.1 or death by any cause, whichever occurs first, as determined by the Investigator.
To evaluate clinical benefit as measured by overall survival (OS).	OS defined as the time from the date of treatment randomization to the date of death by any cause.
To evaluate clinical benefit as measured by time to first subsequent treatment (TFST).	TFST defined as the time from the date of treatment randomization to the date of first subsequent anticancer therapy or death.
To evaluate the safety and tolerability of neoadjuvant niraparib and neoadjuvant platinum-taxane doublet chemotherapy.	Frequency and severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), and dose modification (i.e., interruptions and discontinuations).

Objectives	Endpoints
To evaluate participants' reported overall tolerability toward treatment, overall health status, OC-specific health-related quality of life (HRQoL) and symptoms.	Arranged in order of clinical importance as follows: To determine overall tolerability toward treatment: change over time in frequency and severity of the items on the Patient Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) during neoadjuvant treatment. To determine symptom tolerability: change from baseline in Functional Assessment of Cancer Therapy-Item GP5 [FACT-GP5] during neoadjuvant treatment. To determine overall health status: change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) items (European Organisation for Research and Treatment of Cancer Item Library 136 [EORTC IL136]) pre-IDS. To determine OC-specific HRQoL and symptoms: change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Ovarian Cancer (EORTC QLQ-OV28) gastrointestinal items (European Organisation for Research and Treatment of Cancer Item Library 137 [EORTC IL137]) pre-IDS.
Exploratory	
CCI [redacted]	

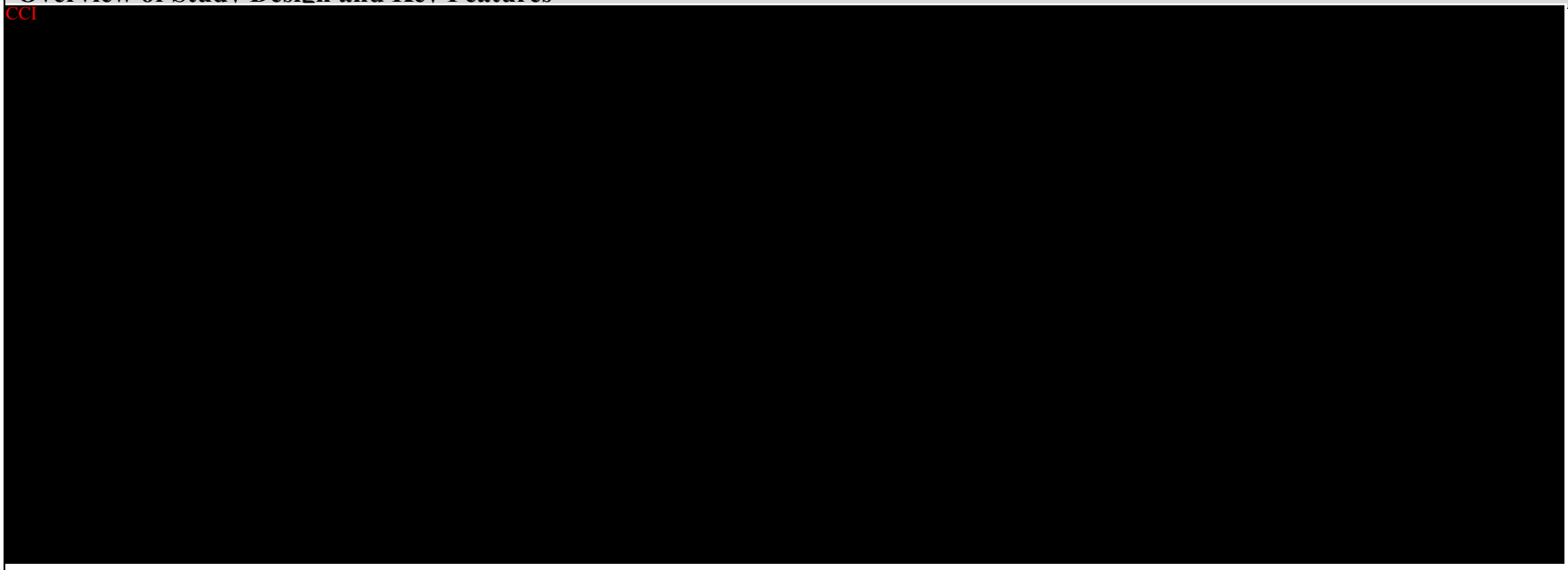
Objectives	Endpoints
CCI [redacted]	
CCI [redacted]	

Objectives	Endpoints
CCI	
CCI	

1.2. Study Design

Overview of Study Design and Key Features

CCI



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 (C6) is optional. If a site chooses to administer Cycle 6 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.
Abbreviations: BRCA=breast cancer gene; 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=participant-reported outcome; QD=once daily; R=randomization; SoC=standard-of-care; TFST=time to first subsequent treatment; xxm=xx months.

Design Features	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 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); (Arm 1 Optional: carboplatin-paclitaxel, unless platinum-taxane not tolerated by the participant) or neoadjuvant niraparib (Arm 2). After 3 cycles of neoadjuvant treatment, the participants will undergo IDS. After IDS, all participants will receive up to three 21-day cycles of adjuvant chemotherapy treatment (Cycles 4, 5 and 6): 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 (Cycle 6) being optional. 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, 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. 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 (up to 36 months).
Study intervention	**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 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 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. **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 (Cycles 4, 5 and 6), 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:** <u>Carboplatin-paclitaxel:</u> Carboplatin will be infused intravenously (IV) 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/m2 on Day 1 of every 21-day cycle. <u>Bevacizumab or bevacizumab biosimilar (optional):</u> Bevacizumab or bevacizumab biosimilar 7.5 mg/kg or 15 mg/kg will be infused IV 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.
Study intervention assignment	CCI [redacted] CCI [redacted] CCI [redacted] Randomization will be stratified based on *BRCA* mutational status (*BRCA*1/2mut vs *BRCA*1/2wt or unknown).
Interim Analysis (IA)	CCI [redacted]

2. STATISTICAL HYPOTHESES

The primary objective of the study is to estimate the treatment effect in pre-IDS ORR. No formal hypothesis testing will be conducted. The difference in pre-IDS ORR between treatment arms and its 80% confidence interval (CI) will be calculated as described in the primary endpoint analysis section (Section 4.2).

The primary analysis will be performed after all pre-IDS scans have been evaluated (about 6 months after last participant first visit [LPFV]). The following endpoints will not be analyzed at this point: PFS, OS, TFST if their maturity is low (<30%), CCI [redacted]
CCI [redacted]
CCI [redacted]

2.1. Multiplicity Adjustment

Not Applicable.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who signed the main ICF.	Study population Screen Failures
Intent-to-treat (ITT)	All randomized participants whether or not randomized treatment was administered.	Study Population Efficacy PRO
Safety	All randomized participants who receive at least one dose of study treatment.	Safety
Pre-IDS Response Evaluable	All participants in the Safety Analysis Set with measurable disease at baseline, excluding participants who received 3 cycles of neoadjuvant treatment whose pre-IDS scan is outside the –7 days window from C3D21.	Efficacy (pre-IDS ORR)
Per Protocol (PP)	All randomized participants who do not have important protocol deviations.	Efficacy
Pharmacokinetic (PK)	All participants in the Safety Analysis Set from whom at least one post-dose PK sample has been obtained and analyzed.	PK

Participants in all analysis sets will be analyzed according to the planned study treatment as there is no distinction between planned and actual study treatment in this study (planned maps to actual).

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The ITT Analysis Set will be used for all study population and efficacy analyses unless otherwise specified (i.e., screening status will be based on the screened population, exposure will be based on the Safety Analysis Set). The Safety Analysis Set will be used for all safety analyses, unless otherwise specified.

For analysis purposes, the run-in chemotherapy treatment is not considered study treatment. Study treatment is any treatment received per the study protocol after randomization.

Stratified analyses will control for the randomization stratification factors (*BRCA* mutational status). For such analyses and reporting of stratification factors, the Randomization and Trial Supply Management System (RTSM) strata levels will be used for all participants randomized unless otherwise specified. In the case of wrong stratification assigned at the time of randomization, the analyses for the wrongly stratified participants will be performed based on the actual data, not the assigned stratum at randomization. Details on derivation of actual *BRCA* strata are provided below:

- The RTSM strata values are calculated from the eCRF entered g*BRCA* and t*BRCA* data (see *BRCA* Strata Value in HRD Status eCRF; this data point is programmatically derived, not manually entered).
- The eCRF values for g*BRCA* and t*BRCA* (based on Myriad test) are entered into the eCRF in the g*BRCA* Status and HRD Status and pages.
- The actual strata values will be assigned as follows:
  - Assign to *BRCA*mut if t*BRCA* = t*BRCA*mut **or** (g*BRCA* = g*BRCA*mut **and** t*BRCA* = t*BRCA*unk)
  - Otherwise, assign to *BRCA*wt/unk [i.e., if t*BRCA* = t*BRCA*wt **or** (t*BRCA* = t*BRCA*unk **and** g*BRCA* ≠ g*BRCA*mut)].

If a stratum contains < 10 participants or < 10 events (for time-to-event endpoints) in total at the time of analysis, then the strata will be pooled and only an unstratified analysis will be conducted.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

Confidence intervals will use 95% level, unless otherwise specified.

Summaries and listings will include all data collected per the Schedule of Assessment (SoA), unless otherwise specified.

Data will be listed and summarized according to the GSK reporting standards, where applicable.

4.1.2. Baseline Definition

For all endpoints, unless otherwise specified, the baseline value will be the latest assessment with a non-missing value prior to C1D1 (in neoadjuvant period), including those from unscheduled visits. If time (pre-dose/post-dose information) is not collected, C1D1 assessments are assumed to be taken prior to first dose and used as baseline. For participants who did not receive study intervention during the study, baseline will be defined as the latest, non-missing collected value. If there are multiple measurements defined as baseline measurements, the mean of them will be used.

For tumor assessments, the RECIST v1.1 scan performed after the run-in cycle of carboplatin-paclitaxel is the baseline scan (per SoA scans prior to the run-in cycle are not expected).

Unless otherwise stated, if baseline data are missing no derivation will be performed and baseline will be set to missing.

4.1.3. Study Day and Reference Date

The efficacy reference date is the date of randomization and will be used to calculate study day for efficacy measures and baseline characteristics, as well as efficacy durations.

The safety reference date is the study intervention start date will be used to calculate study day for safety measures.

Calculated as the number of days from First Dose Date (C1D1):

- Event Date = Missing → Study Day = Missing
- Event Date < First Dose Date → Study Day = Event Date – First Dose Date
- Event Date ≥ First Dose Date → Study Day = Event Date – (First Dose Date) + 1.

Note: The earlier date of first dosing date from each treatment will be considered as first dose date for the participant.

4.1.4. Durations

Unless otherwise specified, time-to-event endpoints will be calculated in months as: (event or censoring date – randomization date + 1)/30.4375.

Durations (e.g., the duration of an AE, etc.) are calculated as the stop date - the start date + 1, unless otherwise specified.

For converting all durations (in days) to weeks, months or years use the following:

- To report in months, divide the number of days by 30.4375,
- To report in weeks, divide the number of days by 7,
- To report in years, divide the number of days by 365.25.

These algorithms return decimal numbers and ignore the actual numbers of days in the months or years between start date and stop date. The “year” used in these algorithms is 365.25 days long, and the “month” is one twelfth of that year.

4.2. Primary Endpoint(s) Analyses

4.2.1. Definition of Endpoint

The primary efficacy endpoint is pre-IDS ORR, defined as the percentage of participants in the analysis set with unconfirmed CR or PR prior to IDS as their best overall response (BOR), evaluated using RECIST v1.1 by the Investigator.

Pre-IDS BOR definition per RECIST v1.1

Pre-IDS BOR is the best response recorded from the start of study treatment administration to the date of IDS, or first documented PD, or initiation of follow-up anticancer therapy (includes drug therapy as captured in the follow-up anticancer therapy page, e.g., platinum-taxane doublet after neoadjuvant treatment, surgery as captured in the follow-up surgery page), whichever is earlier (unconfirmed for the purposes of this study). The order from best to worst for the available responses is CR, PR, SD, PD, and NE, NA (not available/missing).

To be assigned a status of SD as BOR, the minimum time for SD must be met, i.e., follow-up disease assessment must have met the SD criteria at least once after the first dose at a minimum interval of 56 days after randomization.

If the minimum time for SD is not met, BOR will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement, the best response will be PD. Alternatively, participants lost to follow-up after an SD assessment not meeting the minimum time criterion will be considered NE.

Participants in the analysis set with NE or NA as BOR will be assumed to be non-responders.

Table 1 RECIST v1.1 Visit Response for Participants with Measurable Disease (i.e., Target Disease)

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	CR/Non-CR/non-PD/NE	No	PR
SD	CR/Non-CR/non-PD/NE	No	SD
PD	Any	Yes or No	PD
Any	PD[b]	Yes or No	PD
Any	Any	Yes	PD
NE	Non-PD	No	NE
CR	NA[c]	No	CR
PR	NA[c]	No	PR
SD	NA[c]	No	SD

Source: Eisenhaue, 2009.
Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease; NE=not evaluated.
Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
a. See RECIST v1.1 publication for further details on what is evidence of a new lesion.
b. In exceptional circumstances, unequivocal progression in nontarget lesions may be accepted as disease progression.
c. No non-target lesions identified at Screening.

Pre-IDS maximum percent change from baseline in tumor size

The pre-IDS maximum percent change from baseline in tumor size will also be derived. This is defined as the maximum percent change in sum of diameters for all target lesions (SDL) from the baseline sum of diameters from the start of study treatment administration to the date of IDS or first documented PD or initiation of follow-up anticancer therapy (drug therapy, e.g., platinum-taxane doublet after neoadjuvant treatment).

The calculation will be based on the formula:

Maximum percent change from baseline in SDL (%) = (Smallest SDL during the on-treatment period / Baseline SDL - 1) × 100

4.2.2. Main Analytical Approach

Pre-IDS ORR will be analyzed in the ITT Analysis Set. The pre-IDS ORR for each treatment arm will be estimated and its 95% CI calculated using the Clopper-Pearson method. The number and percentage of participants with pre-IDS BOR of CR (unconfirmed), PR (unconfirmed), SD, PD, NE, NA will be summarized.

The difference in pre-IDS ORR between the niraparib and the platinum-taxane doublet chemotherapy neoadjuvant treatments will be estimated and its 2-sided 80% CI calculated using the stratified (*BRCA* mutation stratification factor) Miettinen and Nurminen method [Miettinen, 1985].

Pre-IDS maximum percent change from baseline in tumor size

Maximum percent change from baseline in tumor size (sum of diameter lesions – SDL) will be summarized (median, std, min, max) by treatment arm. A waterfall plot showing maximum percent change from baseline in tumor size by participant will be produced for each treatment arm.

Additionally, a spider plot showing the change in tumor size from baseline over time by participant will be produced for each treatment arm.

4.2.2.1. Sensitivity analyses

Sensitivity Analysis 1 (SA1): The difference in pre-IDS ORR between the two treatment arms will be estimated and its 80% CI calculated using the Mantel-Haenszel test (*BRCA* mutation stratification factor).

Sensitivity Analysis 2 (SA2): An unstratified analysis using the Miettinen and Nurminen method will be conducted.

Sensitivity Analysis 3 (SA3): An analysis as described in Section 4.2.2, but based on the Pre-IDS Response Evaluable Analysis Set will be conducted.

Sensitivity Analysis 4 (SA4): A sensitivity analysis may be conducted in order to assess the pre-IDS ORR using logistic regression evaluating odds ratio between treatment arms, by controlling for the randomization stratification factors.

4.2.3. Subgroup Analyses

The treatment effect will be presented by *BRCA* status (*BRCA*mut vs *BRCA*wt/unk) if the sample size of the groups allows, i.e., if there are at least 10 participants in each treatment allocation group. See Section 4.1.1 for details on participants' *BRCA* status derivation.

4.3. Secondary Endpoint(s) Analyses

Safety endpoint analyses are described in Section 5.8.

4.3.1. Incidence of CA-125 progression per GCIG criteria

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

- Participants with elevated CA-125 pre-treatment and a reduction of CA-125 to within the normal range on study must show evidence of CA-125 ≥2× upper limit of normal (ULN) on 2 occasions at least 1 week apart.
- Participants with elevated CA-125 pre-treatment 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 pre-treatment must show evidence of CA125 ≥2× ULN on study on 2 occasions at least 1 week apart.

Normal range for CA-125 is 0-35 units/mL.

Main Analysis

The percentage of CA-125 progression per GCIG criteria for each treatment arm will be estimated and its 95% exact CI calculated using the Clopper-Pearson method. The difference in CA-125 progression will be estimated and its 95% CI calculated using the stratified (*BRCA* mutation stratification factor) Miettinen and Nurminen method.

4.3.2. Progression Free Survival (PFS)

PFS is defined as the time from the date of randomization to the date of first documented PD per RECIST v1.1 by Investigator assessment, or death by any cause, whichever occurs first.

The censoring rules for PFS at the time of analysis are summarized in Table 2.

Table 2 Censoring rules for PFS analysis

Scenario	Censoring Rule	Outcome
No baseline tumor assessment and no death*.	Date of randomization	Censored
No adequate post-baseline tumor assessments and no death*.	Date of randomization.	Censored
No documented progression and no death.	Date of last adequate tumor assessment.	Censored
Follow-up anticancer therapy initiated without documented progression.	Date of last adequate tumor assessment prior to or on initiation of follow-up anticancer therapy.	Censored
Documented progression or death after ≤ 1 missed or inadequate assessment.	Date of documented progression or death, whichever occurs first.	Event
Documented progression or death after ≥ 2 consecutive missed or inadequate assessments (see Section 7.2.6 for programmatic derivation).	Date of last adequate tumor assessment prior to ≥ 2 consecutive missed or inadequate assessments.	Censored

*If death date < 2nd scheduled assessment date then it counts as an Event, otherwise, if death date ≥ 2nd scheduled assessment date it does not count as an Event.
Note: Adequate tumor assessment is defined as a tumor assessment result that is not NE or NA.
Note: In case of missing baseline or post-baseline tumor assessments, deaths occurring within the <2 missed visit window from randomization will count as events.
Note: Follow-up anticancer therapy includes drug therapy as captured in the follow-up anticancer therapy eCRF page and surgery as captured in the follow-up surgery eCRF page.
Note: If a documented progression and new anticancer therapy occur on the same day, assume the progression was documented first. The outcome is progression (event) and the event date is the date of the assessment of progression.

Main Analysis

The frequency (number and percentage) of participants with an event (PD or death) and participants censored will be presented by treatment arm, together with the reason for censoring. The corresponding listing will also be presented. Reasons for censoring are:

- No documented PD or death at data cut-off:
  - Participant ongoing/at-risk
- Study discontinuation prior to PD or death:
  - Withdrawal of consent
  - Lost to follow-up
- No baseline/post-baseline assessment
- Initiation of follow-up anticancer therapy without documented PD
- Documented PD after 2 or more missing or inadequate post-baseline assessments.

The PFS curve for each treatment arm will be estimated using the non-parametric Kaplan-Meier (KM) product limit estimate method. KM plots will be presented by treatment arm. KM estimates for the median and the first and third quartiles (Q1 and Q3), together with their 95% CIs calculated using the Brookmeyer-Crowley method [Brookmeyer, 1982] will be presented.

The KM PFS rates at 12, 18 and 24 months and their 95% CIs will be presented by treatment arm.

The hazard ratio (HR) will be estimated, and its 95% CI calculated using a stratified (*BRCA* mutation stratification factor) Cox proportional hazards model with exact method for tie handling and randomized treatment as the single covariate.

4.3.3. Overall Survival (OS)

OS is defined as the time from the date of randomization to the date of death due to any cause. Participants without documented death at the time of the analysis will be censored at the last date they were known to be alive. The last known alive date will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

Specifically, for participants not known to have died, the date of last contact will be derived at the analysis cut-off date using the latest complete date among the following:

- Participant assessment dates (blood sampling [laboratory, PK, biomarker], vital signs, ECGs, tumor assessments)
- Start and end date of AEs
- Start and end date of study treatment
- Start date of follow-up anticancer therapies administered after study treatment discontinuation (including surgery)
- Date of contact on survival assessment page for current patient status = alive.

Main Analysis

The OS curve for each treatment arm will be estimated using the non-parametric KM product limit method. KM plots will be presented by treatment arm. KM estimates for the median and the first and third quartiles, together with their 95% CIs calculated using the Brookmeyer-Crowley [Brookmeyer, 1982] method will be presented. The KM OS rates at 12, 24 and 36 months and their 95% CIs will be presented by treatment arm.

The HR will be estimated, and its 95% CI calculated using a stratified (*BRCA* mutation stratification factor) Cox proportional hazards model with exact method for tie handling and randomized treatment as the single covariate.

4.3.4. Time to First Subsequent Therapy (TFST)

TFST is defined as the time from the date of randomization to the date of first subsequent anticancer therapy (includes drug therapy/surgery) or death. Participants who have not

initiated first subsequent therapy or have not died at the time of the analysis will be censored at the last time known to not have received first subsequent anticancer therapy (includes surgery). For participants without EOT (i.e., study treatment not discontinued) this will be their last known alive date. For participants with EOT and no information on receipt of first subsequent therapy this equals the EOT date. For participants with EOT who have knowingly not received first subsequent therapy (i.e., for whom the response to "has the participant received any subsequent therapy/surgery?" is "No" for all relevant visits), this equals the last contact date as captured in the survival assessment eCRF form.

Main Analysis

TFST will be analyzed using the same methodology as PFS.

4.3.5. Patient-Reported Outcomes

PRO-CTCAE and WPAI:GH are to be completed weekly during neoadjuvant chemotherapy and at EOT.

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, and at EOT.

EORTC QLQ-C30 (IL136) and EORTC QLQ-OV28 (IL137) are to be completed at every site visit during the neoadjuvant treatment period, at M1D1 and every 3 cycles for the first 13-14 months, and every 3 months thereafter during niraparib maintenance treatment, and at EOT.

The ITT analysis set will be used for all PRO analyses. For assessment windows for PRO endpoints refer to Appendix Section 7.3.

4.3.5.1. Compliance

The overall compliance and compliance by visit will be summarized for each PRO instrument. Compliance will be reported separately for the neoadjuvant and maintenance periods as part of the secondary and exploratory endpoints respectively. The reasons for missingness will also be reported.

% Overall Compliance = 100 × (number of participants with an evaluable baseline form and at least one evaluable post-baseline form/number of participants expected to complete the baseline form)

% Compliance by Visit = 100 × (number of participants with evaluable form/number of participants expected to have completed a form)

Participants expected to have completed a PRO instrument at an analysis point exclude those missing by design, i.e., due to death, study discontinuation, translation not available.

Evaluable forms are those with at least one non-missing scale or item, depending on the corresponding questionnaire's scoring instructions as defined in the SAP.

To characterize missingness, the number and percentage of participants who did not complete their PRO forms when expected to will be summarized by reason for missingness:

- PRO assessment form not received – missed study visit
- PRO assessment form not received – site staff unable to administer including device malfunction
- PRO assessment form not received – participant too ill
- PRO assessment form not received – unable to accommodate disability or language/comprehension
- PRO assessment form not received – other.

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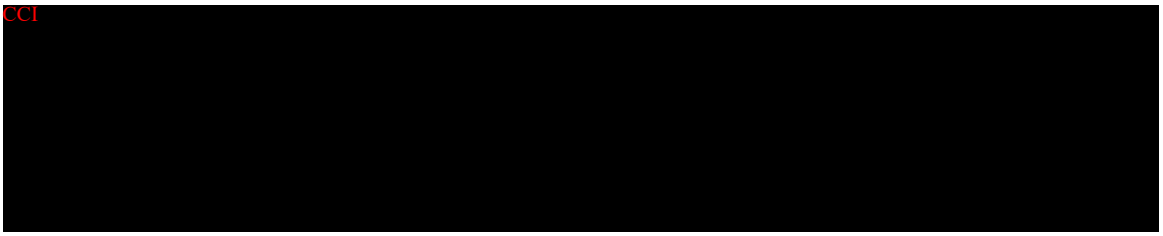

4.3.5.2. PRO-CTCAE

A subset of items from the PRO-CTCAE v1.0 Item Library will be administered to participants (see Study Reference Manual for further details). These are: taste changes, nausea, vomiting, abdominal pain, bloating, constipation, diarrhea, memory, muscle pain, joint pain, fatigue, anxiety, neuropathy, sadness.

The levels and related code values for PRO-CTCAE scoring are shown in Table 3.

Table 3 PRO-CTCAE Levels

	Levels and related code values				
Response scale	**0**	**1**	**2**	**3**	**4**
Frequency	Never	Rarely	Occasionally	Frequently	Almost Constantly
Severity	None	Mild	Moderate	Severe	Very severe
Interference	Not at all	A little bit	Somewhat	Quite a bit	Very much
Present/Absence	No	Yes			

For each PRO-CTCAE item and attribute (frequency, severity, interference, presence/absence), the number and percentage of participants in each response category (0, 1, 2, 3 and 4) will be summarized by scheduled visit and treatment arm.

For each item and attribute, the change from baseline will be assessed by reporting the number and percentage of participants with any worsening in symptoms compared to their baseline score.

4.3.5.3. FACT-GP5

FACT-GP5 is a single item from the FACT-G, which assesses how bothersome the side effects of treatment are for participants.

The number and percentage of participants in each category of FACT-GP5 (0 = Not at all, 1 = A little bit, 2 = Somewhat, 3 = Quite a bit, 4 = Very much) will be reported by scheduled visit and treatment arm. In addition, the number and percentage of participants who moved ≤1, 2, and ≥3 categories with respect to baseline will be reported by scheduled visit and treatment arm. The analyses will be restricted to the neoadjuvant period.

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

The EORTC QLQ-C30 is a 30-item questionnaire used to measure HRQoL in participants with cancer and is composed of both multi-item scales and single-item measures. It includes 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). The EORTC QLQ-C30 uses 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].

A subset of 10 items from the EORTC QLQ-C30 (see Table 4) will be administered and will be referred to as the EORTC IL136, as shown in Table 4.

Table 4 Scoring the QLQ-C30 v3.0

Scale	Abbr.	Number of Items	Item Range*	*Included in IL136*	EORTC QLQ-C30 Item Numbers
Global Health Status/QoL					
Global Health Status/QoL	*QL*	*2*	*6*	*29, 30*	*29, 30*
Functional Scales					
Physical Functioning	*PF*	*5*	*3*	*1 to 5*	*1 to 5*
Social Functioning	*SF*	*2*	*3*	*26, 27*	*26, 27*
Symptom Scales/Items					
Dyspnea	*DY*	*1*	*3*	*8*	*8*

Abbreviations: QoL=Quality of Life.

Questionnaire Scoring

The multi-item EORTC QLQ-C30 domains of interest represent full scales and therefore the usual questionnaire scoring methodology can be applied, as described below.

Scale scores are calculated by averaging items within scales and transforming average scores linearly. The same is done for item scores, only the average equals the item's score. All scales and single-item measures range in score from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning whereas a high score for a symptom scale/item represents a high level of symptomatology or problems.

The principle for scoring these scales is the same in all cases and detailed below:

1. Estimate the raw score by averaging of the items that contribute to the scale.

2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100.

For all scales, the *RawScore* (*RS*) is the mean of the component items:

$$RawScore = RS = \frac{I_1 + I_2 + \cdots + I_n}{n}$$

For QLQ-C30 Global health status/QoL Scale:

$$Score = \left\{\frac{(RS - 1)}{range}\right\} \times 100$$

Thus, a higher score represents a higher ("better") level of health status/QoL.

For QLQ-C30 Functional Scales:

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

Thus, a higher score represents a higher ("better") level of functioning.

For QLQ-C30 Symptom Scales/Items:

$$Score = \left\{\frac{(RS - 1)}{range}\right\} \times 100$$

Thus, a higher score represents a higher ("worse") level of symptoms.

Missing questionnaire data

If there are missing items in a scale, the scale score will be calculated on the completed items if at least 50% of the component items have been completed; otherwise, the scale score is regarded as missing.

Statistical Analyses

Secondary analyses are restricted to the neoadjuvant treatment period.

Summary statistics for observed values and change from baseline (mean, median, std, min, max) will be provided for the scales and items by treatment arm at each scheduled visit.

Additionally, the scale/item score change from baseline will also be summarized in a categorical fashion with respect to a 10-point change. A change of 10 points in IL136 scale score is considered to be the minimum clinically important difference (MCID) [Osoba ,1998]. The categories are:

Definition	Description
For Global Health Status/QoL & functional scales:	
• **Improved**	change from baseline ≥ 10 points
• **Stable**	-10 points < change from baseline < 10 points
• **Worsened**	change from baseline ≤ -10 points
For symptom scales	
• **Improved**	change from baseline ≤ -10 points
• **Stable**	-10 points < change from baseline < 10 points
• **Worsened**	change from baseline ≥ 10 points

The number and percentage of participants in each of the above categories will be summarized by treatment group at each scheduled visit.

MMRM Analysis

Mixed effects models for repeated measures will be used to assess the effect of niraparib compared to platinum-taxane during the neoadjuvant treatment period for the change from baseline in EORTC IL136 scale scores (global health, physical functioning, social functioning, and dyspnea). Participant will be treated as a random effect. All other covariates will be fixed effects. The fixed effects will include treatment, scheduled visit, *BRCA* mutation status (if there are at least 20 participants in each stratum), treatment-by-scheduled visit interaction as well as the respective baseline value for the scale being measured. All scheduled visits in the neoadjuvant period will be included apart from those with excessive missing data at a visit (defined as >75% missing data).

An unstructured covariance matrix will be used to model the within and between participant variance and the Kenward and Rogers approximation [Kenward, 2009] will be used to estimate the degrees of freedom. Restricted maximum likelihood (REML) estimation will be used. The following provides sample code for implementing the MMRM analysis:

```
proc mixed data=EORTC method=reml;
class TRT(ref="PBO") AVISIT SUBJID;
model EORTCCHG = TRT AVISIT TRT*AVISIT BLEORTC BRCASTAT
(conditional)/s ddfm=kr;
repeated AVISIT / type=UN participant=SUBJID;
lsmeans TRT*AVISIT / slice=AVISIT diff alpha=0.05 cl;
run;
quit;
```

where TRT is the randomized treatment, AVISIT is the analysis visit, EORTCCHG is the change from baseline in the EORTC IL136 scale score and BLEORTC is the baseline EORTC 1L136 scale score.

If the fit of the unstructured covariance structure fails to converge, the following repeated covariance structures together with a random effect for participant (random intercept / participant=SUBJID;) will be used in order until convergence is reached: Toeplitz with heterogeneity (TOEPH) and Toeplitz (TOEP). If there are still issues with the fit of the model or estimation of the treatment effects, PARTICIPANT will be treated as a fixed effect.

Least square (LS) means and LS mean differences will be presented by visit and treatment group along with their 95% CIs.

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

The ovarian cancer module (QLQ-OV28) supplements the QLQ-C30, 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). Table 5 summarizes the EORTC QLQ-OV28 scales and component items.

A subset of the EORTC QLQ-OV28 will be utilized (see Table 5) and will be referred to as the EORTC IL137.

The scoring approach for the OC module is identical in principle to that used for the scales/items of the EORTC QLQ-C30. However, the items included in IL137 do not represent full scales and will be analyzed as single items.

Table 5 Scoring the QLQ-OV28

Scale	Abbr.	Number of Items	Item Range	*Included in IL137*	QLQ-OV28 Item Numbers
Functional Scales					
Body Image	BI	2	3	50	50, 51
Attitude to Disease/Treatment	AT	3	3	52, 53	52 to 54
Symptom Scales/Items					
Abdominal/gastrointestinal	AG	7	3	32, 34 to 37	31 to 37
Peripheral Neuropathy	PN	3	3	43	41 to 43

Statistical Analyses

Secondary analyses are restricted to the neoadjuvant period.

The linear transformation of scores, the treatment of missing values, the descriptive statistics to be presented, the classification of scale scores as improved, stable or worsened by 10 points and the use of MMRM to assess the effect of treatment on change from baseline will be the same for the EORTC QLQ-OV28 IL137 as described above for the EORTC QLQ-C30 IL136.

5. EXPLORATORY ANALYSES

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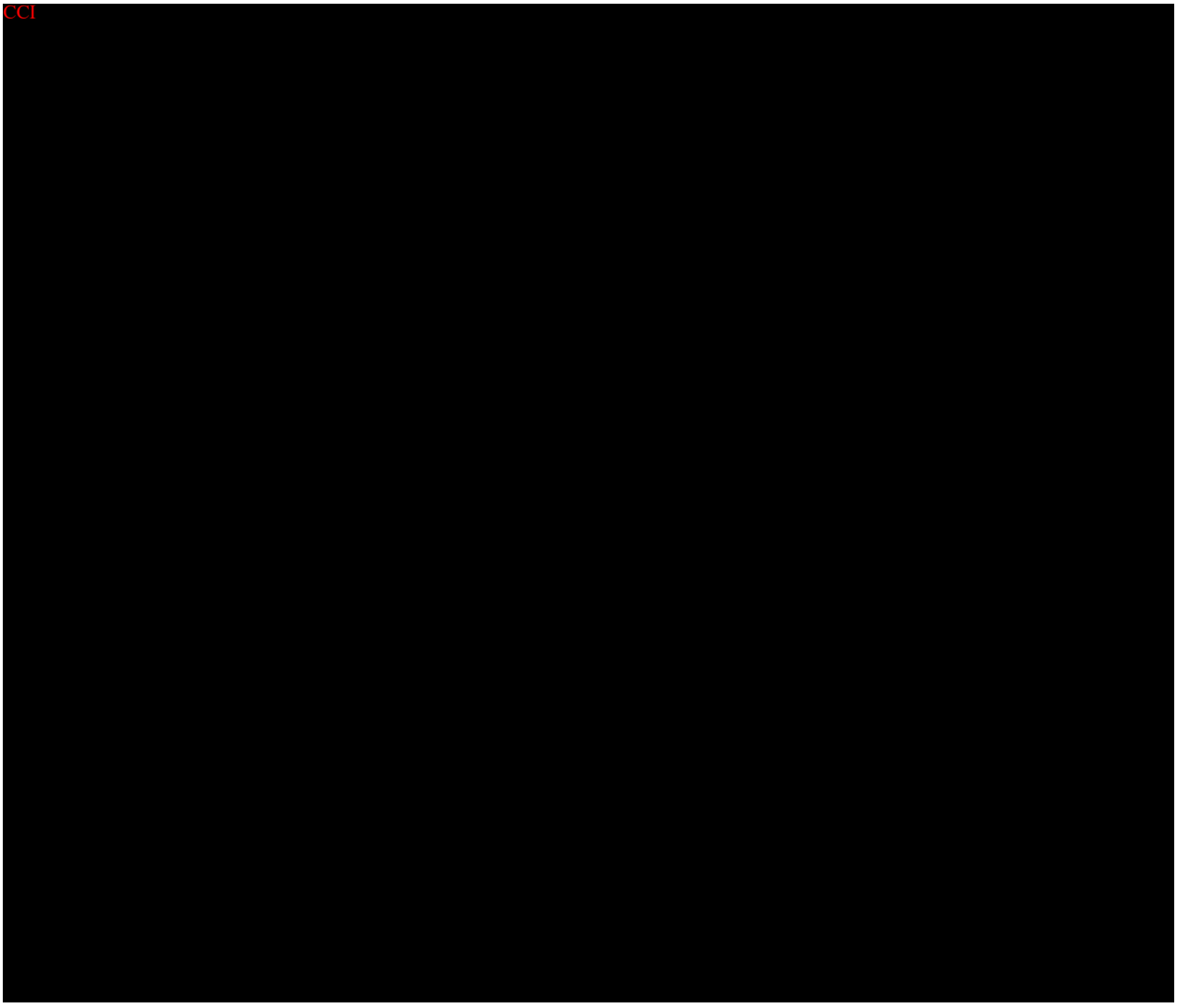

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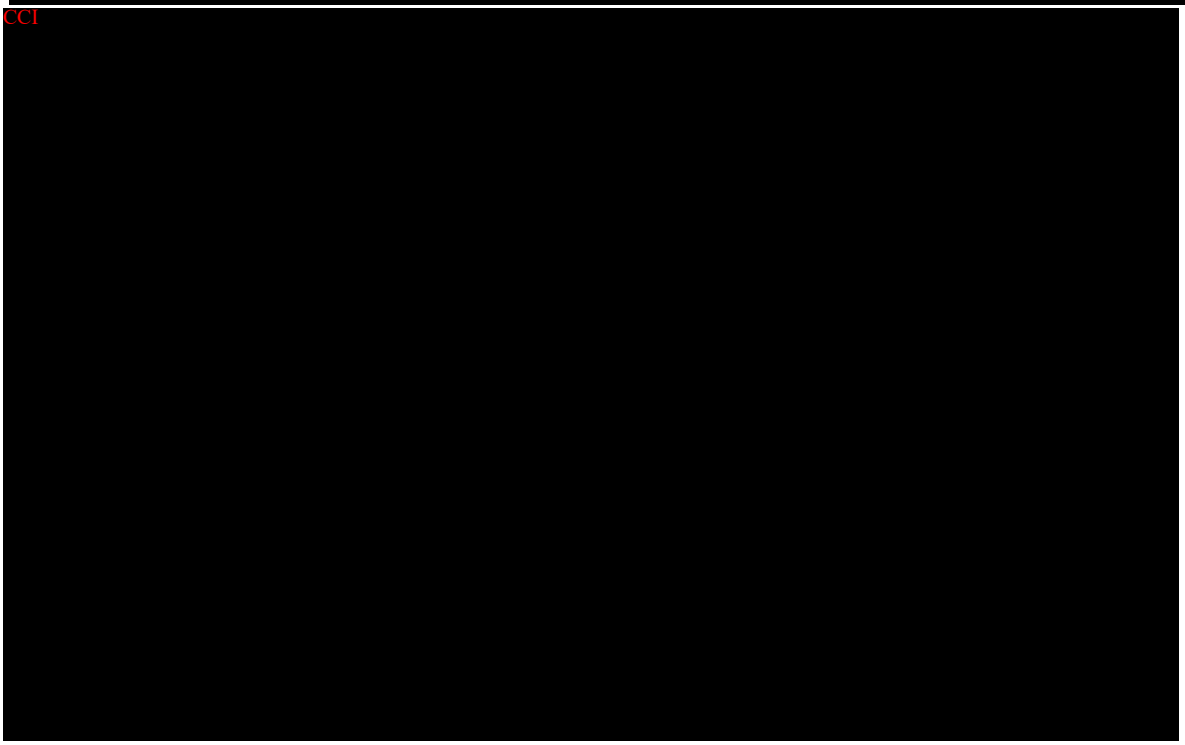

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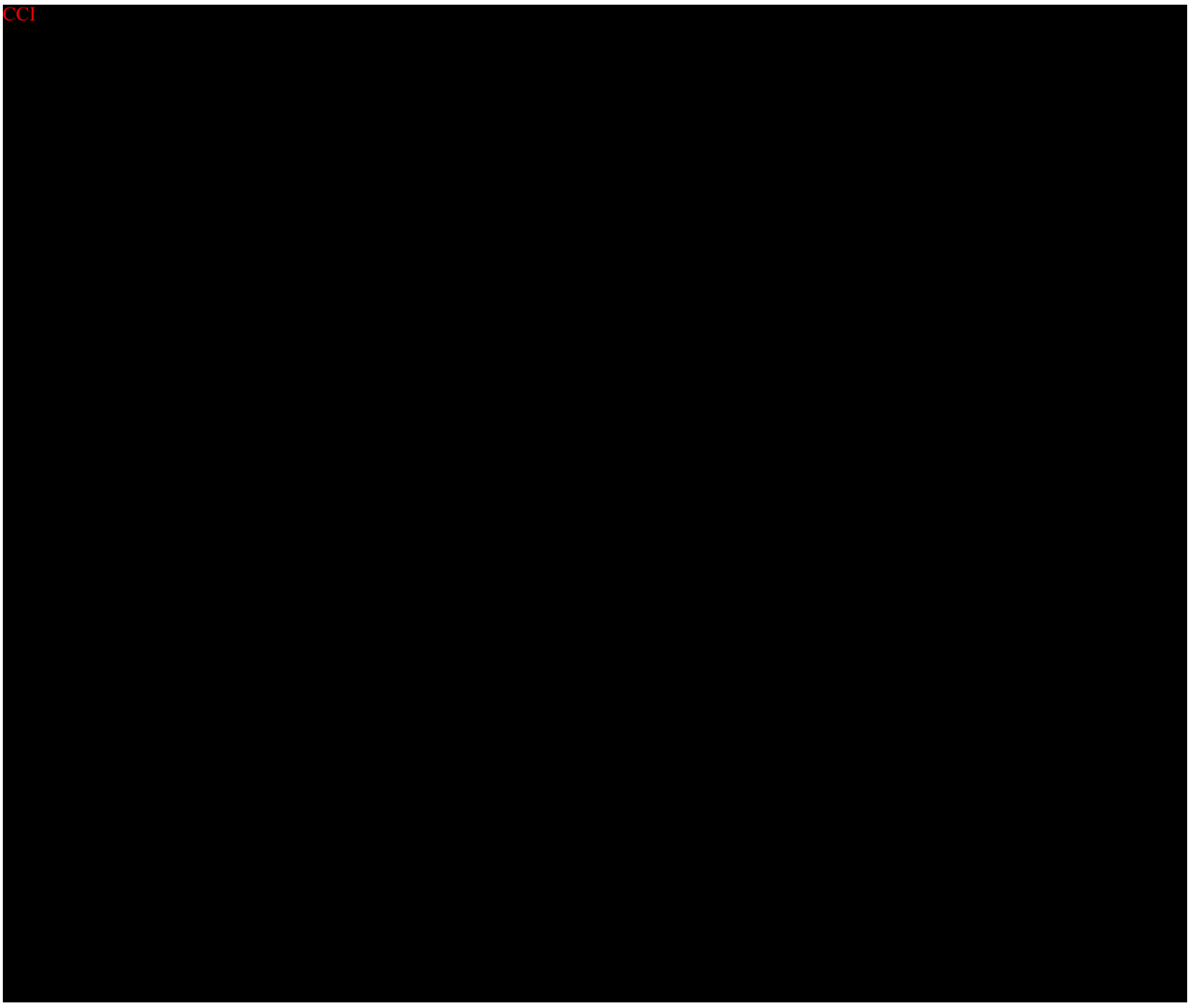

5.8. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

5.8.1. Extent of Exposure

5.8.1.1. Niraparib Treatment Exposure

Duration of treatment

Summaries will be done by treatment arm and treatment period (neoadjuvant, maintenance).

During the neoadjuvant treatment period, the number and percentage of participants beginning 1, 2, or 3 cycles of niraparib treatment will be summarized.

During the maintenance period, the following will be summarized by treatment arm:

- Number and percent of participants initiating 1, 2, 3, …, 12, and >12 cycles.

- Number of cycles started, summarized as a continuous variable.
- Treatment exposure (months), defined as the [last dose date of maintenance treatment - first dose date of maintenance treatment + 1] / 30.4375. Last dose of maintenance treatment equals last cycle entered in the eCRF + 20 days (for ongoing participants) to account for the daily dosing after dispensation or last dose date (for subjects who have discontinued treatment).
- Actual treatment exposure (months), defined as the maintenance treatment exposure minus the duration of dose interruptions.

Treatment Compliance

The following will be summarized by treatment period (neoadjuvant, maintenance) and treatment arm:

- The cumulative actual dose, i.e., the sum of the daily doses consumed (mg), defined as the total number of CCI consumed multiplied by the dosage (mg). The total number of CCI consumed is the sum of the number of CCI dispensed minus the sum of the number of CCI returned by the participant.
- Dose intensity (mg/day), defined as the cumulative actual dose divided by overall treatment exposure (converted to days).
- Relative dose intensity (RDI, %), defined as dose intensity (mg/day) divided by intended dose intensity (mg/day) multiplied by 100, where intended dose intensity is the intended starting dose [dose prescribed in C1D1] (descriptive statistics, as well as number and percentage of participants in the <80%, 80%-105%, and >105% categories).

Dose modifications

Dose reductions and interruptions will be summarized.

Dosing information and CCI counts for each participant will be presented in a data listing.

5.8.1.2. Chemotherapy Treatment Exposure

Duration of treatment

The following will be summarized by treatment arm and treatment period (neoadjuvant, adjuvant):

- Number and percentage of participants initiating 1, 2, 3 cycles.
- Neoadjuvant treatment exposure (months), defined as the [last dose date of neoadjuvant treatment - first dose date + 21] / 30.4375.
- Adjuvant treatment exposure (months), defined as the [last dose date of adjuvant treatment - first dose date of adjuvant treatment + 21] / 30.4375.

Treatment compliance

The following will be summarized by treatment period (neoadjuvant, adjuvant) and treatment arm:

- Cumulative dose (mg/m^2 for paclitaxel/docetaxel/cisplatin, mg for carboplatin), calculated as the sum of all actual doses infused divided by the body surface area.
- Dose intensity (mg/m^2/week for paclitaxel/docetaxel/cisplatin**,** mg/week for carboplatin), calculated as cumulative dose divided by duration of treatment ([last dose date of neoadjuvant/adjuvant treatment - first dose date of neoadjuvant/adjuvant treatment + 21]/7).
- Relative dose intensity (RDI) (%), calculated as dose intensity divided by intended dose intensity × 100.
    - For paclitaxel, cisplatin, docetaxel intended dose intensity (mg/m^2/week) is calculated as (intended dose level/3)/body surface area (intended dose level, body surface area as collected in the study treatment eCRF pages for the first dose of treatment). Further details on intended dose level may be found in the study protocol.
    - For carboplatin, intended dose intensity (mg/week) is calculated by converting the intended dose unit (as collected in the eCRF page for the first dose of treatment) from AUC to mg using Calvert's formula, then dividing by 3:
        - Intended dose (mg) = Intended dose (AUC) × (GFR + 25), where GFR = 0.85 × (140 – age in years) × weight in kg / (72 × serum creatinine (mg/dL))
        - Intended dose intensity (mg/week) = Intended dose (mg)/3.

Dose modifications

Infusion delays and interruptions will be summarized.

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

5.8.1.3. Bevacizumab/Bevacizumab Biosimilar Treatment Exposure

Duration of treatment

The following will be summarized by treatment arm for the overall treatment period (adjuvant + maintenance):

- Number and percentage of participants initiating 1, 2, 3, …, 12, and >12 cycles.
- Number of cycles started summarized as a continuous variable.
- Treatment exposure (months), defined as the [last dose date of bevacizumab/bevacizumab biosimilar treatment - first dose date of bevacizumab/bevacizumab biosimilar treatment + 21] / 30.4375.

Treatment Compliance

The following will be summarized by treatment arm for the overall period (adjuvant + maintenance):

- Cumulative dose (mg/kg), calculated as the sum of all actual doses infused divided by weight.
- Dose intensity (mg/kg/week), calculated as cumulative dose divided by duration of treatment ([last dose date of bevacizumab/bevacizumab biosimilar treatment - first dose date of bevacizumab/bevacizumab biosimilar treatment + 21]/7).
- RDI (%), calculated as dose intensity (mg/kg/week) divided by intended dose intensity (mg/kg/week) × 100, where the intended dose intensity is either (7.5/3) mg/kg/week or (15/3) mg/kg/week.

Dose modifications

Infusion delays and interruptions will be summarized.

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

5.8.2. Adverse Events

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs), Adverse Events of Special Interest (AESI) and other significant AEs will be based on GSK Core Data Standards.

Adverse events will be coded using the latest MedDRA version available at the time of the analysis and grouped by System Organ Class. AEs will be graded by the Investigator according to the NCI-CTCAE v5.0.

Summaries will focus on **treatment emergent adverse events** (TEAEs). TEAEs are defined as AEs with start date on or after the initiation of neoadjuvant study treatment (C1D1) and within 30 days of the last dose of study treatment. AEs with missing date of onset and missing stop date will be considered to have started on the date of initiation of study treatment and will therefore be classified as TEAEs. AEs with missing date of onset and stop date after the initiation of study treatment will be considered to be concomitant. TEAEs will be further classified in the following categories, defined by period of occurrence:

Neoadjuvant TEAEs: From the first dose of study treatment (neoadjuvant, C1D1) to the date of IDS or 30 days after the last dose of neoadjuvant study treatment, whichever is earlier. Events associated with IDS are not included.

IDS TEAEs: From the date of IDS until the first dose of adjuvant therapy or 30 days after the date of IDS, whichever is earlier.

Adjuvant TEAEs: From the first dose of adjuvant therapy until the first dose of maintenance therapy or 30 days after the last dose of adjuvant study treatment, whichever is earlier.

Maintenance TEAEs: From the first dose of maintenance therapy to 30 days after the last dose of maintenance study treatment.

Overall TEAEs: From the first dose of neoadjuvant study treatment (C1D1) to 30 days after the last dose of study treatment.

All AEs, not just TEAEs, will be listed for participants in the Safety analysis set. The listing will include the treatment period of occurrence of the AE and AESI flag.

5.8.2.1. Treatment Emergent Adverse Events (TEAEs)

The number and percentage of participants experiencing a TEAE will be presented by treatment arm and treatment period (neoadjuvant, adjuvant, maintenance, overall), sorted by SOC and PT unless otherwise specified. Participants will be counted once within each SOC or PT. For by-maximum grade summaries, participants experiencing the same TEAE multiple times, with different grade, will only be counted once under the maximum grade recorded. The following summary tables will be produced by treatment arm:

- TEAEs by SOC, PT and maximum grade
- Treatment related TEAEs by SOC, PT and maximum grade (related to any treatment)
- Serious TEAEs by SOC, PT and maximum grade
- Serious TEAEs by SOC and PT (if needed)
- Serious TEAEs by SOC and PT (number of participants and occurrences)
- Serious fatal and non-fatal treatment related TEAEs by Overall Frequency (related to any treatment)
- Common (≥5%) TEAEs by Overall Frequency
- Common (≥5%) Non-serious TEAEs by SOC and PT
- Non-serious treatment related TEAEs by Overall Frequency (related to any treatment)
- TEAEs leading to permanent study treatment discontinuation (by chemo combo, bevacizumab/bevacizumab biosimilar, niraparib, any treatment)
- TEAEs leading to dose reduction (applies to niraparib only)
- TEAEs leading to dose interruption (by chemo combo, bevacizumab/bevacizumab biosimilar, niraparib, any treatment)
- TEAEs leading to dose delay (by chemo combo, bevacizumab/bevacizumab biosimilar, niraparib, any treatment)
- TEAE Overview (include TEAEs, treatment related TEAEs, TEAEs Grade ≥3, treatment related TEAEs Grade ≥3, Serious TEAEs, Serious treatment related TEAEs, TEAEs leading to niraparib dose reduction, TEAEs leading to chemo combo/bevacizumab/bevacizumab biosimilar/niraparib/any treatment dose interruption, TEAEs leading to chemo combo/bevacizumab/bevacizumab biosimilar/niraparib/any treatment dose delay, TEAEs leading to permanent

discontinuation of chemo combo/bevacizumab/bevacizumab biosimilar/niraparib/any treatment, Fatal TEAEs).

For common (≥5%) TEAEs that occurred in strictly 5% of the participants, or above, no rounding for the percentage will be used in terms of 5% threshold, e.g., events with 4.9% incidence rate should not be included in these tables.

Relatedness of TEAE to study treatment will be assessed by the Investigator and captured in the eCRF. In cases where relatedness is missing, the TEAE will be classified as related to study treatment. Treatment related TEAEs will be presented at the treatment arm level (i.e., by relatedness to any treatment component).

5.8.2.2. TEAEs of Special Interest (TEAESI)

The AESIs for this study are myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), or second primary cancer (new malignancies other than MDS or AML). The event search strategy is defined in Table 7.

Each AESI will be summarized by grouped term and PT for the neoadjuvant and overall periods:

- TEAESI by grouped term, PT and maximum grade
- Treatment related TEAESI by grouped term, PT and maximum grade (related to any treatment)
- Serious TEAESI by grouped term, PT and maximum grade
- TEAESI leading to permanent discontinuation of any study treatment
- TEAESI leading to dose modification (interruption/reduction/delay) of any study treatment.

Table 7 Adverse Events of Special Interest

Group Term	MedDRA Criteria for Selection of Preferred Terms[1]
AESI (MDS/AML events)	Myelodysplastic syndrome (SMQ Narrow) Leukemias acute myeloid (HLT)
AESI (new malignancies other than MDS/AML)	• Hematological malignant tumors (SMQ Narrow) • Non-haematological malignant tumors (SMQ Narrow) Note: Selected PTs in the SMQs not considered a second primary malignancy upon clinical/safety team review will be flagged and not used in the event search.

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

5.8.2.3. Deaths

All deaths will be summarized. The summary will include status (death, alive at last contact, follow-up ended, follow-up ongoing), primary cause of death and number of deaths relative to the last dose of study treatment (>30 days, or ≤30 days). A supportive listing will be generated on participants who died.

5.8.2.4. Pregnancy

A listing of participants who became pregnant during the study will be produced.

5.8.3. Additional Safety Assessments

5.8.3.1. ECOG Performance Status

ECOG performance status will be reported in a data listing. A summary of worst-case change from baseline will be provided.

5.8.3.2. Laboratory Data

Laboratory evaluations including the analyses of chemistry, hematology and urinalysis laboratory tests and other screening tests will be based on GSK Core Data Standards. Descriptive statistics (mean, std, median, range) will be used to summarize worst change from baseline in observed value (increase or decrease as applicable).

Summaries of worst-case grade increase from baseline grade will be provided for hematology and chemistry laboratory tests that can be graded by CTCAE v5.0. These summaries will display the number and percentage of participants with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia separately.

For laboratory tests that cannot be graded by CTCAE v5.0, summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst-case post-baseline. If a participant has a decrease to low and an increase to high during the same time interval, then the participant is counted in both the “Decrease to Low” categories and the “Increase to High” categories.

The calculation of worst-case change will use data from both scheduled and unscheduled visits.

Summaries of hepatobiliary laboratory events including possible Hy’s law cases will be provided in addition to what has been described above. The summary will be produced for worst-case post-baseline only.

Possible Hy’s law cases are defined as:

- ALT ≥3×ULN and total bilirubin ≥2×ULN (with direct bilirubin ≥35% of total bilirubin or direct bilirubin missing) or,
- ALT ≥3×ULN and INR >1.5 or missing.

The total bilirubin elevation and/or INR value must occur on or up to 28 days after the ALT elevation.

An e-DISH plot of maximum post-baseline total bilirubin versus maximum post-baseline ALT will be created.

Summary of liver monitoring and stopping events, as well as summary of hepatobiliary laboratory abnormalities will be summarized according to GSK Core Data Standards and will be used to summarize data specific to participants who meet the protocol-specified liver stopping or monitoring events.

If a laboratory value, which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.

- Example 1: 2 Significant Digits = '<x' becomes x – 0.01
- Example 2: 1 Significant Digit = '>x' becomes x + 0.1
- Example 3: 0 Significant Digits = '<x' becomes x – 1

5.8.3.3. Vital Signs

Baseline values of vital signs (temperature, heart rate, systolic blood pressure [SBP] and diastolic blood pressure [DBP]), as well as the worst-case change from baseline will be summarized by treatment arm using n, mean, median, std, minimum and maximum. The determination of the worst-case post-baseline vital signs will consider both scheduled and unscheduled assessments.

A summary of post-baseline worst-case vital signs results relative to baseline with respect to normal range or grade will be presented. The determination of the worst-case post-baseline vital signs will consider both scheduled and unscheduled assessments. Participants with missing baseline values are assumed to have a normal/Grade 0 baseline value.

For temperature and heart rate worst-case will be presented with respect to normal range according to the following normal ranges:

- Temperature: anything ≤35 and ≥38 °C falls outside of normal range
- Heart rate: 50-90 bpm (beats/minute).

For systolic and diastolic blood pressure worst-case increase will be presented with respect to maximum grade according to the following NCI-CTCAE grades:

- SBP (mmHg): Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159), Grade 3 (≥160).
- DBP (mmHg): Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), Grade 3 (≥100).

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

5.8.4. Data Review Committee (DRC) Analyses

The DRC will convene for meetings during the study at the following times:

- After the first 5 participants in the pre-IDS response evaluable population in each arm have undergone their RECIST v1.1 primary endpoint assessment (prior to IDS) to review preliminary safety and efficacy data.
- CCI [redacted]
  CCI [redacted]
- At the primary efficacy analysis to assess if the primary efficacy endpoint, defined as the percentage of participants with unconfirmed CR or PR on study intervention pre-IDS as assessed per RECIST v1.1, has been met.

Additional ad-hoc data reviews by the DRC may also be triggered by any concerns raised by the DRC itself during these meetings.

The following outputs will be produced for DRC review purposes. Safety TEAE summaries will be provided by treatment period (including overall). Listings/graphs marked with * may be provided either as static or through RAPIDO.

1. Subject status (summary)
2. Treatment status (summary)
3. Extent of exposure by study treatment component (summary)
4. Demographic characteristics (summary)
5. Disease characteristics (summary)
6. Pre-IDS overall response rate – based on ITT and pre-IDS evaluable analysis sets (summary grouped by *BRCA* status and overall)
    - Include difference in pre-IDS ORR and 80% CI, and Bayesian predictive probability to assess the futility rule as described in Section 5.9.
7. Overall response (waterfall and spider plots grouped by *BRCA* status and overall)
    - Mark the last pre-IDS assessment in the spider plots.
    - Include data only for pre-IDS assessments in the waterfall plots.
8. TEAE overview
9. TEAEs by SOC, PT and maximum grade (summary)
10. Treatment related TEAEs by SOC, PT and maximum grade (summary)
11. Serious TEAEs by SOC, PT and maximum grade (summary)
12. Serious fatal and non-fatal treatment related TEAEs by Overall Frequency (summary)
13. TEAESIs by category, PT and maximum grade (summary)
14. Serious TEAESIs by category, PT and maximum grade (summary)
15. TEAEs leading to permanent treatment discontinuation of any treatment (summary)
16. TEAEs leading to interruption of any treatment (summary)
17. TEAEs leading to delay of any treatment (summary)
18. TEAEs leading to dose reduction (summary, applies to niraparib only)
19. Summary of deaths
20. All AEs (listing, include column with study period, include chemotherapy run-in AEs for participants in the Safety Analysis Set)*
21. Worst-case change from baseline with respect to grade/normal-range chemistry/hematology laboratory data (summary)

22. Worst-case change from baseline in vital signs (blood pressure & heart rate summary)
23. Change from baseline in CA-125 (line graph)*
24. All laboratory data for participants with values outside of normal range in chemistry/hematology laboratory data (listing)*
25. Liver toxicity events (summary)
26. Overall responses (listing, include *BRCA* status)*
    - Mark the last pre-IDS response assessment in the listing.
27. Reasons for treatment discontinuation (listing, include period at which treatment was discontinued)*
28. IDS surgery details (summary, including outcome datapoints described in Section 5.1).

The population used for each output will be the one identified in the SAP.

5.9. Interim Analyses

CCI

CCI

6. SAMPLE SIZE DETERMINATION

Sample size calculation was performed using CCI

CCI

7. SUPPORTING DOCUMENTATION

7.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the ITT Analysis Set (i.e., screening status will be based on the Screened Analysis Set, treatment status will be based on the Safety Analysis Set).

Analyses will be based on GSK Core and Oncology Data Standards.

7.1.1. Participant Disposition

Participant disposition summaries will include:

- Screening status (participants screened, participants randomized, screen failures and reasons for failure based on the Screened Analysis Set)
- Participant status (ongoing on study treatment, ongoing in follow-up, died, withdrawn from study and reason for study withdrawal)
- Treatment status (ongoing by treatment period, discontinued from all study treatment within the treatment arm and reason for discontinuation of last treatment discontinued based on the Safety Analysis Set)
- Number and percentage of randomized participants belonging to each analysis population (ITT, Pre-IDS Response Evaluable, Safety, Per-Protocol, etc.).

All disposition data will be summarized by treatment arm and overall. For treatment status, participants are considered to have discontinued from a treatment if they have discontinued all treatment components within it.

Participants in the ITT Analysis Set will be summarized by country and site ID.

7.1.2. Demographic and Baseline Characteristics

Demographic characteristics will be summarized by treatment arm and overall and include the following categories:

- Sex: male, female
- Age (years): summary statistics
- Age Group (years): < 18, 18-49, 50-65, ≥65
- Ethnicity
- Race Detail
- Height (cm): summary statistics
- Weight (kg): summary statistics
- ECOG performance status at Screening: 0, 1
- BMI (kg/m^2): summary statistics

Past medical conditions and current medical conditions, including other cancer history, will be summarized.

Disease characteristics at initial diagnosis and at Screening will be summarized by treatment arm and overall, and include the following categories:

- Primary tumor site: ovarian, primary peritoneal, fallopian tube
- Time from initial diagnosis to randomization (weeks): summary statistics
- Cancer stage (FIGO) at initial diagnosis: 0, Stage I A-C, Stage II A-C, Stage III A-C, Stage IV
- *BRCA* status: *BRCA* 1/2 mutated, *BRCA* 1/2 wild type or unknown according to RTSM and Myriad results
- Histologic subtype at initial diagnosis: as captured in eCRF ovarian cancer pathology page
- Tumor grade at initial diagnosis: as captured in eCRF ovarian cancer pathology page
- Metastatic disease sites at screening: as captured in eCRF primary cancer history page.

Summary statistics, unless otherwise indicated, will include mean, standard deviation (std), minimum, median, and maximum. The count and percentage will be computed for the categorical variables.

7.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as "Important" as follows:

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations are captured and categorized in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

Protocol deviations which result in exclusion from the analysis set will also be summarized.

- Data will be reviewed prior to unblinding and freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorized in the protocol deviations ADaM dataset (note these exclusions are not captured in the SDTM dataset).

A separate listing of all inclusion/exclusion criteria deviations will also be provided.

Further details are outlined in the Protocol Deviation Management Plan.

7.1.4. Prior and Concomitant Medications

Concomitant medications are medications, other than study treatment with a start date prior to, on or after the start of the first dose of neoadjuvant study treatment (C1D1) and a stop date within 30 days after the last dose of study treatment.

Derivations or concomitant medications will use imputed dates where possible/necessary. If the medication start date is prior to the treatment start date and the stop date is missing, or start and stop date are missing, then the medication will be classified as concomitant.

Prior and concomitant medications will be coded using the WHO Drug dictionary. The summaries of prior and concomitant medications will be provided by ingredient; i.e. multi-ingredient medications will be summarized for each individual ingredient rather than a combination of ingredients. The summary will be created using ingredient base names, i.e. ingredients with the same base name but different salt will appear under one base name in the summary. Anatomical Therapeutic Chemical (ATC) classifications will not appear in the summary. Each participant will be counted once within a unique ingredient.

7.1.4.1. Follow-Up Anticancer Therapy

Follow-up anticancer therapy will be coded using the WHO Drug dictionary. The number and percentage of participants initiating follow-up anticancer therapy will be summarized by therapy type as collected in the eCRF (including radiotherapy, surgery) and treatment arm. The summary will include the time from study treatment discontinuation to start of follow-up therapy (weeks).

Follow-up anticancer therapy will be listed.

7.1.4.2. Duration of Follow-Up

The duration of follow-up will be summarized in months (median, interquartile range [IQR: Q3-Q1], min, max) by treatment arm. Follow-up time is defined as:

Follow-up time (months) =
(date of death or last known date alive – date of randomization + 1) / 30.4375.

7.1.5. Additional Analyses Due to the COVID-19 Pandemic

A participant is defined as having a suspected, probable or confirmed COVID-19 infection during the study if the answer is “Confirmed”, “Probable” or “Suspected” to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF. Numbers of participants with a suspected, probable or confirmed COVID-19 infection, and of COVID-19 test results will be summarized by treatment arm.

7.2. Appendix 2 Data Derivations Rule

7.2.1. Criteria for Potential Clinical Importance

7.2.1.1. Laboratory Data

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern.

7.2.1.2. Vital Signs

See Section 5.8.3.3 for the grading of systolic and diastolic pressure and for the normal ranges for temperature and heart rate.

7.2.2. Study Period

The study periods/flags for calculation of concomitant medications and safety assessments are defined in the Sections below. **For analysis purposes, study treatment is considered any treatment received after randomization.**

7.2.2.1. Study Period

Study Period	Definition
Chemotherapy Run-in	**Chemotherapy Run-in** Study Treatment Start Date ≤ Date ≤ min(**Chemotherapy Run-in** Study Treatment Stop Date + 30 days, **Neoadjuvant** Study Treatment Start Date - 1) *For participants who do not start neoadjuvant treatment, set neoadjuvant treatment start date to Infimum
Neoadjuvant	**Neoadjuvant** Study Treatment Start Date ≤ Date ≤ min(**Neoadjuvant** Study Treatment Stop Date + 30 days, **IDS** date - 1) *For participants who do not get IDS, set IDS date to Infimum
IDS	**IDS** Date ≤ Date ≤ min(**IDS** Date+30 days, **Adjuvant** Treatment Start Date - 1) *For participants who do not start adjuvant treatment, set adjuvant treatment start date to Infimum
Adjuvant	**Adjuvant** Study Treatment Start Date ≤ Date ≤ min (**Adjuvant** Study Treatment Stop Date + 30 days, **Maintenance** Study Treatment Start Date - 1) *For participants who do not start maintenance treatment, set maintenance treatment date to Infimum
Maintenance	**Maintenance** Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date + 30 days
Overall	Study Treatment Start Date (of **any** study treatment) ≤ AE Start Date ≤ Study Treatment Stop Date (of **any** study treatment) + 30 days

7.2.2.2. Study Period for Concomitant Medication

Study Period	Definition
Concomitant	Study Treatment Start Date ≤ Start Date ≤ Study Treatment Stop Date + 30 days

NOTES:

Refer to Section 7.2.5 for Handling of Partial dates for concomitant medication. Use the rules in that table if concomitant medication date is completely missing.
If Start Date < Study Treatment Start Date and Stop Date is missing, then Study Period = Concomitant
If Start and Stop Date are missing, then Study Period = Concomitant
If Start Date is missing and Stop Date > Study Treatment Start date, then Study Period = Concomitant

7.2.2.3. Study Periods for Treatment Emergent Adverse Events

Study Period	Definition
Overall	Study Treatment Start Date (of any study treatment) ≤ AE Start Date ≤ Study Treatment Stop Date (of any study treatment) + 30 days
Neoadjuvant	**Neoadjuvant** Study Treatment Start Date ≤ AE Start Date ≤ min (IDS date - 1, **Neoadjuvant** Study Treatment Stop Date + 30 days)
IDS	**IDS** Date ≤ AE Start Date ≤ min (**Adjuvant** Treatment Start Date - 1, **IDS** Date+30 days)
Adjuvant	**Adjuvant** Study Treatment Start Date ≤ AE Start Date ≤ min (**Maintenance** Study Treatment Start Date - 1, **Adjuvant** Study Treatment Stop Date + 30 days)
Maintenance	**Maintenance** Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 30 days

If AE start date is missing, then the AE will be considered to be treatment emergent with start date falling in the overall and neoadjuvant periods.
If AE start date and stop dates are missing, then the AE is treatment emergent with start date falling in the overall and neoadjuvant periods.
If AE start date is missing and stop date > treatment start date, then the AE is considered to be treatment emergent with start date falling in the overall and neoadjuvant periods.
Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

7.2.2.4. End of Study Definition

The end of the study (EOS) is defined as the date of the last scheduled procedure shown in the Clinical Study Protocol's Schedule of Events (refer to Table 5 of the protocol) 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.

7.2.3. Assessment Windows

Generally, for data summaries by visit, scheduled visits with nominal visit description, as well as the worst-case post-baseline will be displayed. Unscheduled visits will not be displayed or slotted into a visit window but will be included in the derivation of worst-case post-baseline assessment. All unscheduled visits will be displayed in the listing.

For PRO endpoints, the following windowing will be applied.

Table 8 Neoadjuvant period: PRO-CTCAE/WPAI:GH/FACT-GP5 windowing

Visit	Scheduled days from baseline (nominally C1D1*)	Window (days)
C1D8	7	4-10
C1D15	14	11-17
C2D1	21	18-24
C2D8	28	25-31
C2D15	35	32-38
C3D1	42	39-45
C3D8	49	46-52
C3D15	56	53-59

*C1D1 is the first dose of study treatment (nominal).

Table 9 Neoadjuvant period: EORTC-IL136/IL137 windowing

Visit	Scheduled days from baseline (nominally C1D1*)	Window (days)
C2D1	21	14-28
C3D1	42	35-49

*C1D1 is the first dose of study treatment (nominal).

Table 10 Maintenance period: FACT-GP5/EORTC-IL136/137 windowing

Visit	Scheduled weeks from maintenance treatment start (nominally M1D1*)	Window (weeks)
M4D1	9	6-12
M7D1	18	15-21
M10D1	27	24-31
M13D1	36	33-39
M17D1	45	42-48
M20D1	54	51-57
M24D1 (schedule change after M20D1)	62	59-65
M28D1	74	71-77
… continue as above		

*M1D1 is the first dose of maintenance treatment.

7.2.4. Multiple Measurements at Any One Analysis Time Point

For laboratory tests on a study day, if more than one assessment is taken on the same day, the test from a central laboratory will be taken over the test from a local laboratory (if this is relevant and data are captured from both central and local laboratories). If multiple assessments are taken from the same type of laboratory, the worst case will be used. For continuous change from baseline summaries, the mean of the measurements will be used.

7.2.5. Handling of Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>

Partial dates will be displayed as captured in participant listing displays.
However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study periods or for specific analysis purposes as outlined below.
Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of AEs), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in OS analysis dataset.

</td></tr>
<tr><td>Adverse Events</td><td>

Partial dates for AE recorded in the eCRF will be imputed using the following conventions:

<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
If month and year of start date = month and year of study intervention start date, then
If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail	

		• If year of start date = year of study intervention start date, then
		  • If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
		  • Else set start date = study intervention start date.
		• Else set start date = January 1.

	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	No Imputation
	Completely missing start/end date	No imputation
Concomitant Medications/Procedures	• Partial dates for any concomitant medications recorded in the eCRF will be imputed using the following convention:	

	Missing start day	If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = 1st of month.
		Else if study intervention start date is not missing:
		• If month and year of start date = month and year of study intervention start date, then
		  • If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
		  • Else set start date = study intervention start date.
		• Else set start date = 1st of month.

	Missing start day and month	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing:

Element	Reporting Detail	

		• If year of start date = year of study intervention start date, then
		  • If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
		  • Else set start date = study intervention start date.
		• Else set start date = January 1.

	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation
	Note: If imputed date is greater than study end date or death date, then earliest of these dates will be used as an end date.	
Exposure	• Partial dates will not be imputed. • Completely missing dates will not be imputed.	
Death date	If a participant is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last complete known to be alive date +1 from the database (as collected in the long-term follow-up eCRF page) and the death date using the available information provided: • For missing day only – use the 1st of the month • For missing day and month – use the 1st of January	

7.2.6. Extended Time without a PFS Assessment

Tumor scans are obtained within 7 days prior to C1D1, at C3D21 (±7 days), at M1D1 (-14 days), every 3 months (±7 days) for the first year of maintenance therapy, every 6 months (±14 days) for the second year and yearly thereafter.

The definition of 2 missed/inadequate consecutive visits varies according to the scan schedule and is defined by matching the last adequate tumor assessment (LATA) prior to an event (PD/death) to a scheduled visit using the midpoint as described in Table 11. LATA on or before the midpoint is assigned to the scheduled visit prior to it. LATA after the midpoint is assigned to the scheduled visit after it.

Table 11 Tumor Assessment Windowing

Assessment Schedule	Scheduled visit -1-2 weeks (7-14 days)	Scheduled visit (from randomization)	Scheduled visit +0-1 weeks (0-7 days)	Midpoint (floor for non-integers)
Neoadjuvant	8 weeks	9 weeks	10 weeks	(M1D1 weeks from randomization)/2 + 4weeks
Maintenance	M1D1-14days	M1D1	M1D1+0days	M1D1+1.5months -3days
	M1D1+3months -7days	M1D1+3months	M1D1+3months +7days	M1D1+4.5months
	M1D1+6months -7days	M1D1+6months	M1D1+6months +7days	M1D1+7.5months
	M1D1+9months -7days	M1D1+9months	M1D1+9months +7days	M1D1+10.5months
	M1D1+12months -14days †	M1D1+12months	M1D1+12months +14days †	M1D1+15months
	M1D1+18months -14days †	M1D1+18months	M1D1+18months +14days †	M1D1+21months
	M1D1+24months -14days †	M1D1+24months	M1D1+24months +14days †	M1D1+30months
	M1D1+36months -14days †	M1D1+36months	M1D1+36months +14days †	M1D1+42months
	M1D1+48months -14days †	M1D1+48months	M1D1+48months +14days †	M1D1+54months

*M1D1 = first dose of maintenance treatment.

†Any event occurring after LATA + T2, is considered to have occurred after 2 consecutive missed assessments, where T2 is defined as follows:

- If LATA prior to event is within (M1D1 weeks from randomization)/2 + 4 weeks, T2 = 2×(M1D1 weeks from randomization in days) + 3 months =

2×(M1D1 weeks from randomization in days) + 92 days + 14 days=2×(M1D1 weeks from randomization in days) + 106 days.

- If LATA prior to event is after (M1D1 weeks from randomization)/2 + 4 weeks and on or before M1D1+1.5 months, T2 = 3 months×2+21 days = 218 days.
- If LATA prior to event is after M1D1+1.5months and on or before M1D1+10.5 months, T2 = 3 months×2+14 days = 197 days.
- If LATA prior to event is after M1D1+10.5months and on or before M1D1+21 months, T2 = 3 months + 6 months +28 days = 302 days.
- If LATA prior to event is after M1D1+21months and on or before M1D1+42 months, T2 = 6 months + 12 months + 28 days = 576 days.
- If LATA prior to event is after M1D1+42 months, T2 = 12 months×2+ 28 days = 759 days.

7.3. Appendix 3 Population Pharmacokinetic Analysis Methodology

Niraparib plasma concentration-time data may be analyzed by population PK methods using a nonlinear mixed-effects modeling approach. The key objective of this analysis is to predict individual PK parameter values for niraparib.

If done, the analysis will be performed by, or under the direct auspices of, CPMS, GSK using the currently supported versions of all software packages. The population PK analysis will be performed using NONMEM (ICON Solutions) and PsN, or another software platform deemed appropriate. Graphical displays and data summary will be produced using R (The R Foundation for Statistical Computing).

Participant data will be collected in the eCRF and will be transmitted into a validated database by GSK data management. Derived/processed variables will be provided by or under the guidance of Clinical Programming. Plasma samples will be analyzed using approved analytical methodology. Data will be transferred electronically to data managers to be processed and stored in the GSK database. GSK or a designated third party will generate the NONMEM input dataset.

Previously combined niraparib PK data may be merged with the PK data in Study 213357 in order to provide a pooled NONMEM data set.

Post hoc or empirical Bayes estimates will be derived applying the current population PK model to the study-specific dataset with the MAXEVAL=0 option. If the corresponding model diagnostics indicate that this population PK model is appropriate to represent the niraparib data from this study, then individual PK parameter estimates will be based on the current population PK parameter values.

If the parameter set of the current population PK model applied to the Study 213357 dataset results in substantial bias or if a further exploration of the covariate effect in the Study 213357 population is deemed necessary, the parameters of the current population PK model will be re-estimated for the Study 213357 PK data alone and/or for a pooled dataset before generating the individual PK parameter estimates. Certain parameter values may be fixed to the value in the current population PK model, if they cannot be estimated with sufficient precision within the Study 213357 PK population. Covariates not available for the Study 213357 PK Population but present in the current population PK model may be removed from the Study 213357 population PK model. Lastly, a model refinement step, if needed, will include, but may not be limited to, a qualification and possible modification of the model's random effect structure.

The model development and final model will be supported and qualified using the following criteria where appropriate:

- Scientific plausibility of parameter estimates
- Goodness of fit plots
- Relative standard errors (RSE) of the parameter estimates
- Objective function value

- Distribution and shrinkage of random effects
- Successful minimization and execution of covariance step
- Condition number (ratio of the largest and smallest eigenvalue of the covariance matrix
- Visual predictive check Bootstrap (if deemed necessary/feasible).

The PK parameter values will be listed and summarized. If done, the analysis will be performed by, or under the direct auspices of, CPMS, GSK, using the currently supported versions of all software packages. These analyses will be performed using R (The R Foundation for Statistical Computing), NONMEM (ICON Solutions) with PsN, or another software platform deemed appropriate.

7.4. Changes from Protocol Defined Analyses

- The analysis sets do not fully align to the corresponding version of the protocol and have been redefined in the SAP. The SAP is to be followed.
- For WPAI:GH, the protocol defines a maintenance period endpoint that is not defined in the SAP due to data for WPAI:GH not being collected during the maintenance period per SoA.

7.5. List of Abbreviations

Abbreviation or Specialist Term	Explanation
AE	adverse event
AESI	adverse event of special interest
AML	acute myeloid leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AUC/$AUC_{0-\infty}$	area under the concentration-time curve/AUC from time zero extrapolated to infinity
BRCA	breast cancer gene
*BRCA*m	breast cancer gene mutated
CA-125	cancer antigen 125
CI	confidence interval
CPMS	Clinical Pharmacology Modeling and Simulation
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
Cx	cycle number
CL/F	apparent clearance following oral dosing
CxDx	Cycle x Day x
DCR	Disease Control Rate
DBP	diastolic blood pressure
DRC	Data Review Committee
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

Abbreviation or Specialist Term	Explanation
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-GP5	Functional Assessment of Cancer Therapy-Item GP5
GCIG	Gynecological Cancer InterGroup
GFR	glomerular filtration rate
GSK	GlaxoSmithKline
HCRU	healthcare resource utilization
HR	hazard ratio/homologous recombination
HRD	homologous recombination deficiency
HRd	homologous recombination-deficient
HRQoL	health-related quality of life
IA	interim analysis
ICF	informed consent form
ICU	intensive care unit
IDS	interval debulking surgery
IQR	interquartile range
IV	intravenous(ly)
ITT	intent-to-treat
KM	Kaplan-Meier
LATA	last adequate tumor assessment
LPFV	last participant first visit
MCID	minimum clinically important difference
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
mPFS	median progression-free survival
MxDx	Cycle x Day x during maintenance treatment period
NACT	neoadjuvant chemotherapy
NCI	National Cancer Institute
NIH	National Institutes of Health
NVRD	no visible residual disease
OC	ovarian cancer
OS	overall survival

Abbreviation or Specialist Term	Explanation
ORR	overall response rate
pCR	pathological complete response
PD	progression of disease/pharmacodynamics
PFS	progression-free survival
PK	pharmacokinetic(s)
PP	per protocol
PR	partial response
PRO	participant-reported outcome
PRO-CTCAE	Participant Reported Outcomes-Common Terminology Criteria for Adverse Events
PsN	Perl Speaks NONMEM
PT	preferred term
QD	once daily
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
REML	restricted maximum likelihood
RDI	relative dose intensity
RTSM	Randomization and trial supply management
SAE	serious adverse event
SAF	safety
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	stable disease
SDF	survival distribution function
SDL	sum of lesion diameter
SMQ	Standardized MedDRA Query
SoA	Schedule of Assessments
SoC	standard of care
SOC	system organ class
std	standard deviation
TEAE	treatment-emergent adverse event
TFST	time to first subsequent treatment
ULN	upper limit of normal

Abbreviation or Specialist Term	**Explanation**
Vss/F	apparent volume of distribution after oral administration
WHO	World Health Organisation
WPAI:GH	Work Productivity and Activity Impairment – General Health

7.6. Trademarks

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None

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MedDRA
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SAS
WHO

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