Title Page

A RANDOMIZED PHASE 3 DOUBLE-BLINDED STUDY COMPARING THE EFFICACY AND SAFETY OF NIRAPARIB TO PLACEBO IN PARTICIPANTS WITH EITHER HER2-NEGATIVE BRCA-MUTATED OR TRIPLE-NEGATIVE BREAST CANCER WITH MOLECULAR DISEASE BASED ON PRESENCE OF CIRCULATING TUMOR DNA AFTER DEFINITIVE THERAPY (ZEST)

Brief Title:	Efficacy and Safety Comparison of Niraparib to Placebo in Participants with HER2-Negative *BRCA*mut or Triple-Negative Breast Cancer with Molecular Disease Based on Presence of ctDNA
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Study Phase:	Phase 3
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Medical Monitor name and contact can be found in local study contact information document.

Sponsor Signatory:	Erin Hofstatter, MD Group Senior Medical Director, Oncology Clinical Development/Synthetic Lethality, GSK
Approval Date:	28 Nov 2023

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 04	28 Nov 2023	TMF-17007234
Amendment 03	02 June 2023	TMF-16097940
Amendment 02 FRA-1	13 Feb 2023	RPS-CLIN-050203
Amendment 02	05 Oct 2022	TMF-14887215
Amendment 1 FRA-1	22 Feb 2022	TMF-14472256
Amendment 1 DEU-4	07 Jan 2022	TMF-14373986
Amendment 01/ Amendment 01 DEU-3	07-Oct-2021	TMF-13772769/ TMF-14011986
Amendment DEU-2	10-Sep-2021	TMF-13986489
Amendment DEU-1	26-Jul-2021	TMF-13891990
Amendment GBR-1	30-Apr-2021	TMF-12903338
Original Protocol (00)	25-Jan-2021	TMF-11716064

Amendment 04

This amendment is considered substantial based on the criteria defined set forth in Article 10(s) of Directive 2001/20/EC of the of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Overall Rationale for the Current Amendment:

The protocol has been amended to add Post-Analysis Continued Treatment (PACT) language to allow eligible participants to receive niraparib after the final analysis data cut-off.

List of main changes in the protocol and their rationale:

Section # and title	Description of Change	Brief Rationale
Headers, title page, abbreviations, Protocol Amendment Summary of Changes, List of Abbreviation.	Headers and title page were updated with new document number and amendment information; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment; minor corrections and formatting adjustments, and to add clarification and/or remove discrepancies.	Editorial changes as needed.
Section 1.1 Synopsis Table 1 Objective and Endpoints Section 3 Objectives and Endpoints and Estimands	Niraparib plasma concentration no longer applicable	PK is no longer being analyzed due to the limited number of samples that were collected prior to stopping enrollment that are evaluable.

Section # and title	Description of Change	Brief Rationale
Synopsis Section 1.1 Section 1.3 Schedule of Activities Section 4.1 Overall Design	Added guidelines for participants who continue treatment after the data cut-off (DCO) date of planned final analysis/database closure	To provide continued treatment options to participants still deriving clinical benefit from treatment when the DCO is reached.
Section 2.2.5 Niraparib	Information added for niraparib	To provide information on the use of niraparib
Section 4.1 Overall Design Table 12: Summary of Patient Management Under Protocol Amendment 04	Visit schedule clarified for PACT Phase	Clarification for study conduct under PACT.
Section 4.4 End of Study Definition Section 6.7 Treatment After the End of the Study	Added definition for end of study (EOS)	Clarification for study conduct under PACT Phase for definition of the EOS.
Section 6.1.1 Niraparib	Information added on dispense of Niraparib under current amendment.	Clarification for study conduct under PACT
Section 6.7.1 Continued Access to Study Intervention	Clarification for access to treatment during PACT Phase	Clarification included regarding treatment following transitions to PACT Phase.
Section 8.5.1 Time Period and Frequency for Collecting AE and SAE Information	Included additional content to include information on collection of safety information via paper forms	Language added for safety reporting requirements under PACT Phase of study. Clarification regarding study conduct outlining study requirements/assessments under PACT Phase for participants receiving access to study treatment (including procedures) following EOS.
Section 10.5 Appendix 5: Regulatory, Ethical, and Study Oversight	Included additional content to describe management of data captured in CRF.	Language added to outline changes to CRF reporting under PACT Phase of study.

Section # and title	Description of Change	Brief Rationale
Considerations	Management of data breaches and its communication to respective parities	Text added as per EU CTR requirement.
Section 10.8 Appendix 8: AEs and SAEs	Included additional content to describe management of SAEs/AESIs/AEs/Overdose/Pregnancy under PACT Phase	Language added for management of SAEs/AESIs/AEs/ Overdose/Pregnancy PACT Phase of study.
Section 10.9 Appendix 9: Pregnancy Initial Notification Form Section 10.10. Appendix 10: Study pregnancy follow up form. Section 10.11 Appendix 11: Serious Adverse Event (SAE) Reporting Form	Addition of Pregnancy initial notification (Section 10.9) form, Study pregnancy follow up form (Section 10.10), and serious adverse reporting form (Section 10.11)	Study Reference Manual (SRM) document is no longer being used; thus, forms previously contained in the SRM added to the protocol.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title

A Randomized Phase 3 Double-Blinded Study Comparing the Efficacy and Safety of Niraparib to Placebo in Participants with Either HER2-Negative *BRCA*-Mutated or Triple-Negative Breast Cancer with Molecular Disease Based on Presence of Circulating Tumor DNA after Definitive Therapy (ZEST)

Brief Title

Efficacy and Safety Comparison of Niraparib to Placebo in Participants with HER2-Negative *BRCA*mut or Triple-Negative Breast Cancer with Molecular Disease Based on Presence of ctDNA

Rationale

Study 213831 was designed as a study of niraparib as treatment for participants with tumor breast cancer susceptibility gene mutated (t*BRCA*mut, which includes participants with germline *BRCA*mut [g*BRCA*mut] and/or somatic *BRCA*mut [s*BRCA*mut]) human epidermal growth factor receptor 2−negative (HER2−) breast cancer or tumor *BRCA* wild-type (t*BRCA*wt) triple-negative breast cancer (TNBC) who have molecular disease based on the presence of circulating tumor DNA (ctDNA) levels after completion of definitive therapy, including all of the following, if indicated: neoadjuvant treatment, surgery, adjuvant radiotherapy, and adjuvant chemotherapy; end of definitive therapy is defined as the date of completion of curative-intent surgery, adjuvant chemotherapy, or adjuvant radiotherapy, whichever was last.

For patients with Stage I, II, IIIA, IIIB, or operable IIIC breast cancer, treatment includes surgical removal of the primary tumor, with lymph node dissection as required [Cardoso, 2019; NCCN, 2020]. Although patient survival after surgery can be improved with adjuvant local and systemic therapy, the risk of recurrence in many patients with breast cancer remains high ([Steeg, 2016], reviewed in [Coakley, 2019]). Once definitive therapy is complete, there is no standard-of-care surveillance or treatment for patients with TNBC, beyond clinical monitoring, until metastatic disease presents. Similarly, for patients with hormone receptor positive (HR+)/HER2− breast cancer on adjuvant endocrine therapy, there is no standard of care surveillance or additional treatment until metastatic disease presents. Once the disease becomes metastatic, the 5-year survival rates are 11.5% for TNBC and 30.4% for HR+/HER2− breast cancer [SEER, 2019].

Current tumor markers to determine the risk of recurrence after definitive therapy, such as carcinoembryonic antigen, cancer antigen 27-29, and cancer antigen 15-3, lack sensitivity and are typically used only in the metastatic setting [Kokko, 2002; Lumachi, 1999; Mariani, 2009]. To identify the patient population at high-risk of recurrence, current efforts are directed at identification of molecular detectable disease, as measured by the presence of ctDNA. Several studies in multiple cancer types, including breast cancer, have shown that molecular detectable disease can be identified using liquid biopsies by tracking tumor mutations in ctDNA and the presence of ctDNA has been

demonstrated to be predictive of clinical or radiological relapse [Coombes, 2019]. Currently, there is no standard of care for patients who have detectable ctDNA following their last intervention (surgery or adjuvant therapy) but who have not yet developed radiologic or clinically evident metastatic disease.

The single-agent efficacy of 2 poly(ADP-ribose) polymerase (PARP) inhibitors, olaparib and talazoparib, has been demonstrated in patients with g*BRCA*mut HER2− breast cancer, including patients with g*BRCA*mut TNBC, in the locally advanced (talazoparib) and metastatic (olaparib and talazoparib) settings [Litton, 2018; Robson, 2017] and in patients with s*BRCA*mut metastatic breast cancer (olaparib) [Tung, 2020].

Studies in TNBC support homologous recombination deficiency (HRD) status as a predictor of response to treatment. HRD testing classifies tumors as either positive for a deficiency in homologous recombination DNA repair (homologous recombination deficient [HRd]) or without a defect in this pathway (homologous recombination proficient [HRp]). In patients with TNBC, including g*BRCA*wt TNBC, HRd disease is frequent [Chopra, 2020] and has been associated with improved response to anticancer treatment [Sharma, 2018; Staaf, 2019; Telli, 2016; Zhao, 2017]. Efficacy of PARP inhibitors has been observed in patients with HRd breast cancer. Patients with early HRd breast cancer treated with neoadjuvant olaparib in combination with paclitaxel had a pathological complete response rate of 55.1%, compared with 48.6% in patients treated with paclitaxel/carboplatin [Fasching, 2021]. In patients with HRd metastatic TNBC treated with veliparib plus cisplatin, longer progression-free survival was observed compared to treatment with cisplatin alone [Sharma, 2020]. In a study of olaparib as neoadjuvant treatment in patients with treatment-naïve TNBC, in which 18 of 32 patients obtained an objective response (56.3%), HRd TNBC was associated with response; 16 of 18 responders (88.9%) had homologous recombination mutations and/or *BRCA* methylation compared with 4 of 14 nonresponders (28.6%) [Eikesdal, 2020]. In a study of neoadjuvant rucaparib in patients with untreated localized TNBC, 70% of whom had HRd cancers, HRDetect-high status was associated with ctDNA suppression [Chopra, 2020].

Clinical activity of niraparib as neoadjuvant treatment in t*BRCA*mut HER2− breast cancer has been demonstrated [Han, 2019]. Additionally, niraparib has demonstrated antitumor efficacy in ovarian cancer beyond *BRCA*mut disease. Results from prior niraparib studies in ovarian cancer indicate a consistent continuum of clinical benefit across biomarker-defined subpopulations and that the benefit of niraparib treatment extends beyond patients with *BRCA*mut disease [Gonzalez-Martin, 2019; Mirza, 2016; Moore, 2019].

Based on these findings, Study 213831 will assess niraparib in participants with t*BRCA*mut HER2− breast cancer (including TNBC) or t*BRCA*wt TNBC who have molecular detectable disease, as determined by the presence of detectable ctDNA, until participants relapse with locally recurrent or metastatic disease. Given the substantial prevalence of HRd disease in TNBC and the expected particular sensitivity to PARP inhibition in these patients [Chopra, 2020], HRD status will be assessed in tumor tissue of t*BRCA*wt TNBC participants, and the primary efficacy analysis in t*BRCA*wt TNBC participants will be based on the HRd subpopulation, followed by testing of the overall cohort of t*BRCA*wt TNBC participants. As of the date of decision to stop enrollment in the ZEST study, this is no longer applicable**.**

Objectives and Endpoints and Estimands

As a result of the decision to stop enrollment in the ZEST study, safety and tolerability of niraparib are being assessed as the primary endpoint and will use the Safety (SAF) Population; efficacy endpoints are considered exploratory. Estimands are not applicable for the primary endpoint.

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluation of safety and tolerability of niraparib	The incidence of TEAEs, SAEs, and AESIs; TEAEs leading to death, TEAEs leading to dose modifications, and TEAEs leading to discontinuation will be assessed. Clinically relevant laboratory parameters, vital signs, ECOG performance status, and use of concomitant medications will be collected and evaluated as defined in the Statistical Analysis Plan (SAP).
Exploratory	
Evaluation of the efficacy of niraparib relative to placebo as measured by disease-free survival (DFS)	DFS is defined as the time until disease recurrence, measured from the time of randomization to the earliest date of assessment of disease recurrence or death by any cause, as assessed by Investigator using RECIST v1.1.
Evaluation of distant recurrence-free survival (DRFS)	DRFS is defined as the time from randomization to the first detection of distant metastasis or death by any cause as assessed by Investigator using RECIST v1.1.
Time to first subsequent therapy (TFST)	TFST is defined as the time from randomization to the date of the first anticancer therapy used subsequent to the date of the endpoint DFS or death by any cause.
Time to first subsequent chemotherapy	Time to first subsequent chemotherapy is defined as the time from randomization to the date of the first systemic chemotherapy used subsequent to the date of the endpoint DFS or death by any cause.
Time to symptomatic progression	Time to symptomatic progression is defined as the time from randomization to the date of symptomatic progression, which either coincides with or is subsequent to the date of the endpoint DFS. Symptomatic progression includes any of the following: • Development of a skeletal-related event: pathologic fracture, spinal cord compression, or need for surgical intervention or radiation therapy (including palliative radiotherapy) to the bone • Initiation of a new systemic anticancer therapy for cancer pain progression or worsening of disease-related symptoms • Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.

Objectives	Endpoints
Evaluation of the efficacy of niraparib relative to placebo as measured by invasive disease-free survival (IDFS)	IDFS will be assessed as per definition included in STEEP 2.0 [Tolaney, 2021] (see Section 8.3.7 of the protocol).
Evaluation of the efficacy of niraparib relative to placebo as measured by invasive breast cancer-free survival (IBCFS)	IBCFS will be assessed as per definition included in STEEP 2.0 ([Tolaney, 2021]; See Section 8.3.8)

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Abbreviations: AE=adverse event; ctDNA=circulating tumor DNA; DFS=disease-free survival; DRFS=distant recurrence-free survival; ECOG=Eastern Cooperative Oncology Group; IBCFS=invasive breast cancer-free survival; IDFS=invasive disease-free survival; PD=progressive disease; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TFST=time to first subsequent therapy; CCI [redacted]

Overall Design

Study 213831 was designed as a multicenter, multicohort, Phase 3, double-blinded, placebo-controlled study comparing the safety and efficacy of niraparib to placebo in participants who are 18 years and older with either HR+/HER2− t*BRCA*mut breast cancer or TNBC with any *BRCA* mutation status who have detectable ctDNA following completion of definitive therapy including all of the following, if indicated: neoadjuvant treatment, surgery, adjuvant radiotherapy, and adjuvant chemotherapy (as outlined in the inclusion/exclusion criteria). The study will include 2 separate cohorts: a t*BRCA*mut HER2− breast cancer (including TNBC) cohort (Cohort 1) and a t*BRCA*wt TNBC cohort (Cohort 2); end of definitive therapy is defined as the date of completion of curative-intent surgery, adjuvant chemotherapy, or adjuvant radiotherapy, whichever was last.

As a result of assessment of feasibility of study completion (i.e., the study was unable to randomize patients in the planned timeframe based on randomization projections as the study had lower-than-expected rates of ctDNA-positivity and a much higher-than-expected proportion of patients with a ctDNA-positive [ctDNA+] test showing

radiographically detectable disease during screening assessments), a decision was made by the Sponsor to permanently stop enrollment into the ZEST study, which was communicated on 25 April 2023 (i.e., the date of decision to stop enrollment). As of the date of this communication, no further randomizations were approved by the Sponsor.

A final data cut-off (DCO) date represents the end of data collection for the planned final analyses as described in the statistical analysis plan (SAP). Once the final DCO date has been reached, the clinical study database will be closed to new data. Before the DCO is reached all participants will continue assessments as per SOA Table 4, Table 5, and Table 6. Once the last participant consents to Protocol Amendment 04 (or withdraws) or meets any protocol-defined stopping criteria (Section 7), the study will transition to PACT.

Following the DCO date, Study 213831 will move to the PACT Phase, where the study will remain open for the following:

1) **Continued access to study treatment (niraparib) for participants who continue to derive clinical benefit from study treatment as judged by the Investigator and do not meet any protocol-defined study treatment stopping criteria (Section 7); participants may also choose to discontinue study treatment at any time and**
2) **Surveillance scans for participants as outlined under Protocol Amendment 04 until stopping criteria are met (Section 7).**

For more details regarding PACT, refer to Section 6.7.1.

Although the clinical study database will be closed at the time of the final DCO date, the study remains open until the end of the study definition is reached. The end of study (EOS) is defined as the date of the last visit of the last participant in the study or last scheduled procedure for the last participant in the study.

Participants on study as of the date of the decision to stop enrollment should be managed under Protocol Amendment 03 as outlined in Table 11 until Protocol Amendment 04 implementation. Upon implementation of Protocol Amendment 04, participants should be managed following Table 12.

Participants randomized to treatment on the ZEST study may discontinue treatment and be offered scans above standard of care, while some previously specified assessments are now discontinued. As a result of stopping enrollment, Prescreening is stopped for new patients and study assessments should be discontinued with the exception of those outlined in Table 4 and Table 5 for those participants in prescreening as of the date of the decision to stop enrollment.

Participants in Prescreening can no longer enter Screening and any participants currently in Screening as of the date of the decision to stop enrollment can no longer be randomized and should follow Table 12.

For participants randomized in the ZEST study and on treatment as of the date of the decision to stop enrollment, the study was unblinded centrally and participants should be managed as outlined in Table 6. As of the date of the decision to stop enrollment, PK sample collection is also discontinued along with the PK substudy.

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Participants will initially enter a Prescreening Period for confirmation of detectable ctDNA. For participants with detectable ctDNA, the Prescreening Period is followed by the Screening Period (Day -42 to Day -1) for completion of the remaining Screening assessments. It is recommended that the Screening Period start within 14 days of a confirmed ctDNA-positive result, provided all submitted prescreening tissue samples are of adequate quality per central review.

Eligible participants in Cohorts 1 and 2 are then randomized to either niraparib or placebo. For Cohort 1, a Safety Run-in as well as a pharmacokinetic (PK) substudy will be performed. The Safety Run-in will include the first 40 randomized participants receiving concomitant endocrine therapy. The PK substudy will include at least the first 40 randomized participants receiving endocrine therapy at sites participating in the PK substudy. Additional participants may be included in the PK substudy so that 6 participants per endocrine therapy are included, if feasible.

The Niraparib/Placebo Treatment Period is followed by an End of Treatment (EOT) Visit occurring within 7 days of last dose, a Safety Follow-up Visit 30 (+7) days after last dose, and Post-treatment Follow-up with assessments every 90 (±14) days for 2 years after the last dose and every 180 (±14) days thereafter.

Patient-reported outcomes will be collected approximately every 28 days (aligned with the regular participant monitoring schedule) during the Treatment Period, at the EOT Visit, at the Safety Follow-up Visit, and at the first 2 Post-treatment Follow-up assessments.

ctDNA Prescreening:

Participants must sign a ctDNA Prescreening informed consent form (ICF) consenting to collection of tumor tissue samples for ctDNA assay design and tumor *BRCA* (t*BRCA)* and HRD testing as well as blood samples for ctDNA testing. Sufficient archival tumor tissue to establish the ctDNA platform and to perform t*BRCA* and HRd testing CCI [redacted]) is a requirement for study entry to enable this testing. This ctDNA Prescreening, utilizing the Signatera test for ctDNA, requires an archival tissue sample from the primary tumor, including pathology reports for all tumor tissue samples, a blood sample for whole exome sequencing (WES), and subsequent ctDNA blood samples, as described in Table 2 and Table 3.

As a result of the decision to stop enrollment, prescreening procedures will be stopped, including ctDNA testing, except as outlined in Section 1.3, Table 4, and Table 5. Ongoing prescreen participants who are ctDNA-negative and <12 months from end of definitive therapy as of the date of the decision to stop enrollment may continue prescreening procedures as outlined above. Upon receiving a detectable ctDNA result by

the Signatera test, these participants will not receive further ctDNA tests and will proceed according to Table 4. Prescreen participants who are ctDNA+ as of the date of the decision to stop enrollment will follow Table 5. Participants who are deemed prescreen failures under previous versions of the protocol will not be reconsented and will not return for any prescreening procedures**.**

Participants in prescreening will have ctDNA testing performed with a maximum of 18 tests over a period of up to 6 years after end of definitive therapy for participants with a known *BRCA*mut (TNBC or HR+) and a maximum of 10 tests performed over a period of up to 2 years for participants with TNBC *BRCA*wt/unknown, as described in Table 13.

Under Protocol Amendment 02, participants who are deemed prescreen failures under previous versions of the protocol due to negative ctDNA test results may have the opportunity to re-enter prescreening if they meet all eligibility criteria in this protocol amendment, meet staging criteria as outlined in Prescreening criterion P2, and remain within the prescreening testing duration windows described in Prescreening criterion P4 (also see Table 14).

Participants under ongoing Prescreening at the time of implementation of Protocol Amendment 02 are eligible for additional ctDNA testing provided they continue to meet all eligibility criteria in this protocol amendment and remain within the prescreening testing duration windows described in Prescreening criterion P4. (Also see Table 14)

A participant can move to the Screening Period once detectable ctDNA is confirmed in Prescreening, provided all submitted prescreening tissue samples are of adequate quality per central review. ctDNA results will be blinded after randomization.

BRCA Tumor Mutational Status Testing:

During ctDNA Prescreening, tumor tissue samples from all participants will be collected for confirmatory central t*BRCA* testing for eligibility considerations using the CCI [redacted]

Participants with HR+/HER2− breast cancer must have a known and documented deleterious or suspected deleterious t*BRCA*mut (either s*BRCA* or g*BRCA* positive) and meet all other prescreening eligibility criteria to qualify for ctDNA Prescreening and must have been on a stable regimen of endocrine therapy for a minimum of 3 months prior to randomization. Participants with HR+/HER2− breast cancer who have t*BRCA*mut confirmed by central testing will be eligible for Cohort 1; if central testing does not confirm a t*BRCA*mut in HR+/HER2− participants, they will not be eligible for the study. Participants with TNBC who have centrally confirmed t*BRCA*mut will be eligible for enrollment in Cohort 1, and those who are t*BRCA*wt or who have undetermined t*BRCA* status will be eligible for enrollment in Cohort 2. Note that the confirmatory central t*BRCA* test does not distinguish between somatic and germline *BRCA* mutations and does not replace standard germline testing.

As a result of the decision to permanently stop enrollment, no further *tBRCA* testing CCI [redacted] will be conducted for any participants, regardless of ctDNA status. All participants randomized prior to the date of the decision to stop enrollment have had confirmatory central *tBRCA* testing completed by CCI [redacted] under previous versions of the protocol.

Tumor HRD Status Testing:

Tumor tissue samples collected at Prescreening will be used for centralized testing using the CCI [redacted] to classify participants in Cohort 2 by HRD status.

As a result of the decision to permanently stop enrollment, no further HRD status assessment using the CCI [redacted] will be conducted for any patient, regardless of ctDNA status. All participants randomized prior to the date of the decision to stop enrollment have had HRD assessment testing by CCI [redacted] completed under previous versions of the protocol.

Screening Period:

As a result of the decision to permanently stop enrollment, participants can no longer enter screening. Participants currently in screening as of the date of the decision to stop enrollment that decide to remain on study will follow Table 5.

During the Screening Period, participants will sign the main study ICF and complete all remaining assessments required to determine eligibility for the study. The Screening Period is within 6 weeks of Cycle 1/Day 1 and it is recommended to start within 14 days of a confirmed ctDNA-positive result, provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (unless otherwise specified in the Schedule of Activities [SOA]) are required to be repeated if they fall outside of 6 weeks prior to first dose.

All participants are required to have documented presence of ctDNA, central confirmation of t*BRCA*mut status, and no evidence of overt recurrent/metastatic disease prior to being randomized 1:1 to either niraparib or placebo.

Randomization and Stratification:

As of the date of the decision to stop enrollment, no further randomizations were approved by the sponsor.

Participants in Cohort 1 will be stratified based on the following factors:

- Time from last intervention to randomization (<6 months versus ≥6 months). Time of last intervention is defined as the date of most recent oncological surgery, date of last adjuvant chemotherapy, or date of last radiotherapy fraction, whichever occurred later.
- HR status (positive versus negative)
- Prognostic Stage of breast cancer (Stage I/II versus Stage III) (see Appendix 13)

Participants in Cohort 2 will be stratified based on the following factors:

- Time from last intervention to randomization (<6 months versus ≥6 months). Time of last intervention is defined as the date of most recent oncological surgery, date of last adjuvant chemotherapy, or date of last radiotherapy fraction, whichever occurred later.
- Prior use of adjuvant capecitabine (yes versus no)
- Prognostic Stage of breast cancer (Stage I/II versus Stage III) (see Appendix 13)

Safety Run-in Period (Cohort 1):

As of the date of the decision to stop enrollment, Safety Run-in is no longer applicable. A total of 40 participants were randomized in the study.

A Safety Run-in Period will be conducted in the first 40 randomized participants in Cohort 1 who are taking endocrine therapy (anastrozole, letrozole, exemestane, and tamoxifen, with or without ovarian function suppressing agents). All participants receiving concomitant endocrine therapy need to have been on a stable regimen of endocrine therapy for a minimum of 3 months prior to randomization. While on study, the endocrine regimen can be interrupted or discontinued as clinically indicated. During the Treatment Period, the endocrine regimen may be exchanged for another regimen after discussion with the GSK Medical Monitor, but the regimen may not be changed during the Safety Run-in Period or the PK substudy.

CCI

As of the date of the decision to stop enrollment, assessment by an IDMC is no longer needed due to enrollment being permanently stopped and the study being centrally unblinded**.**

Study Conduct:

As the date of the decision to stop enrollment, several study procedures described below are no longer applicable. As of Protocol Amendment 04, participants should be managed as outlined in Section 1.3 and Table 12. For participant management prior to DCO, refer to Section 1.3 for additional details. For participant management after DCO, please refer to Section 6.7.

Participants who meet all eligibility criteria for study screening will have to sign the main ICF for this study before starting the screening assessments to participate in the study. Once all screening assessments are completed, eligible participants will be randomized in a 1:1 ratio to receive niraparib or placebo.

Clinic visits will occur on Day 1 of each cycle (Table 3). Hematology laboratory values will be monitored weekly for the first 28-day cycle of the Niraparib/Placebo Treatment Period, and blood pressure (BP) and heart rate (pulse) will be monitored weekly for the first two 28-day cycles of the Niraparib/Placebo Treatment Period. If participants are unable to attend clinic visits on Cycle 1/Day 1 (postdose), Cycle 1/Day 15, and Cycle 2/Day 1 (postdose), they must have assessments for these visits performed through at-home nursing on the date the visit would have occurred. If participants are unable to attend clinic visits on Cycle 1/Day 8, Cycle 1/Day 22, Cycle 2/Day 8, Cycle 2/Day 15, and Cycle 2/Day 22, they must have the assessments for these visits performed either through a local laboratory/clinic or through at-home nursing on the date the visit would have occurred. As of the date of the decision to stop enrollment, at-home nursing services will no longer be offered.

All participants are required to undergo tumor imaging as provided below and all imaging data acquired with the purpose of tumor assessment must be submitted to the Imaging Vendor for Central Review. As of the date of the decision to stop enrollment, imaging does not need to be submitted to the imaging vendor for central review. Imaging will be conducted for ongoing participants as outlined in Section 1.3, Table 4, Table 5, and Table 6 The preferred imaging method is intravenous (IV) contrast-enhanced computed tomography (CT), and a bone scan. The same imaging method and anatomical coverage should be used throughout the study.

- Baseline:
  - An IV contrast-enhanced-CT scan of the chest/abdomen/pelvis and a bone scan will be conducted within 42 days (6 weeks) prior to randomization (as outlined in Table 3).
  - If IV CT contrast cannot be used (e.g., sensitivity to CT contrast or contrast shortage): Noncontrast CT of the chest and IV contrast-enhanced magnetic resonance imaging (MRI) of abdomen/pelvis, and a bone scan.

    If both IV CT and IV MRI contrast cannot be used, or if renal insufficiency: noncontrast CT of chest/abdomen/pelvis and a bone scan. If MRI is performed at Baseline, it should be preferentially continued throughout the study. If brain metastasis is suspected, IV contrast-enhanced MRI is preferred over IV contrast-enhanced CT for imaging of the brain.
  - On study: An IV contrast-enhanced CT scan of the chest, abdomen, and pelvis (or IV contrast-enhanced MRI of abdomen and pelvis and noncontrast CT of chest, if MRI performed at Baseline) will be conducted every 12 weeks (84±7 days) from date of randomization for the first 2 years and every 24 weeks (168±7 days) thereafter, or more frequently as clinically indicated (unscheduled), until Investigator assessment of disease recurrence using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Bone scans should only be performed postbaseline if clinically indicated. If brain metastasis is suspected, IV contrast-enhanced MRI is preferred over IV contrast-enhanced CT for imaging of the brain.

If a participant discontinues study treatment for any reason other than disease recurrence, death, withdrawal of consent, or loss to follow-up, then scans should continue at the specified intervals until disease recurrence is confirmed.

Each participant will have an EOT Visit at the time of discontinuation from study treatment, a Safety Follow-up Visit 30 (+7) days after last dose, and Post-treatment Follow-up with assessments every 90 (±14) days for 2 years after the last dose and every 180 (±14) days thereafter, which will continue until death or the end of study data collection (provided that this allows the opportunity for completion of all follow-up assessments). Information regarding subsequent anticancer treatments (including regimen and number of cycles), as well as the date of any subsequent progressive disease (ie, for determination of progression on next anticancer therapy), hospitalization, and other supportive care and procedures (eg, surgery or radiation), and survival status will be collected during these assessments.

Reporting of safety events will begin at the time of the ctDNA Prescreening ICF signature date only for events related to ctDNA and WES blood sample collection procedures. All adverse events (AEs) and serious adverse events (SAEs) will be collected and recorded for each participant from the day of signing the main study ICF until 30 days after last dose of study treatment or start of new anticancer therapy. All AEs and SAEs experienced by a participant, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the participant is lost to follow-up, or until the participant has died. All SAEs assessed by the Investigator as related to the study treatment and all AEs of special interest, regardless of causality, will be collected and reported until study closeout, or as otherwise indicated. Any pregnancies that occur within 180 days post-treatment will be reported.

Participants will continue to receive their assigned treatment until disease recurrence as assessed by RECIST v1.1, death, withdrawal of consent, loss to follow-up, or until unacceptable toxicity. Those participants who have completed 39 cycles (approximately 3 years) without evidence of recurrence will have the option to either continue treatment or stop treatment at that time. If available, participants continuing niraparib treatment at the time of final analysis may be offered the option to continue to receive niraparib treatment. Dose interruptions, reductions, and/or treatment discontinuation may be implemented at any time according to the dose modification guidelines in this protocol (Section 6.4) and under the discretion of the Investigator. As of the date of the decision to stop enrollment, this is no longer applicable.

Biomarker Strategy

As of the date of the decision to stop enrollment, sample collection for the purposes of exploratory biomarker analysis was stopped as outlined in Section 1.3.

CCI [redacted].

In Cohort 1 (t*BRCA*mut/HER2−), participants with HR+ disease must have a known and documented deleterious or suspected deleterious t*BRCA*mut (either germline or somatic) to qualify for ctDNA Prescreening. All participants, including those with TNBC, will have their t*BRCA* status confirmed by a central laboratory prior to randomization. Participants with HR+/HER2− breast cancer must have a centrally confirmed t*BRCA*mut to be eligible for the study.

Participants in Cohort 2 will have the HRD status of their tumor determined by centralized testing CCI [redacted]

Participants in Cohorts 1 and 2 will be tested for ctDNA using blood samples at the following time points:

- During ctDNA Prescreening: According to the schedule summarized in Table 2, Table 13, and Figure 3
- At Cycle 1/Day 1: Predose

- During Niraparib/Placebo Treatment Period: Every 12 weeks from randomization until disease recurrence, to monitor niraparib efficacy and development of recurrence and/or metastasis.

Exploratory biomarker analyses to identify factors important for niraparib therapy may be pursued. Blood samples for exploratory biomarker testing will be collected at the time points specified in Table 3. CCI [redacted]

If a participant discontinues study treatment for any reason other than disease recurrence per RECIST v1.1, death, withdrawal of consent, or loss to follow-up, then ctDNA sample collection should continue at the specified intervals until disease recurrence is confirmed.

Further Biomedical Research

The Sponsor will conduct Further Biomedical Research on specimens and data collected during this study. This research may include genetic and genomic analyses, gene expression profiling, proteomics, metabolomics, and the measurement of other analytes after this study is completed. It may also include analysis of histological and/or clinical images and data. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from properly consented participants and as per local regulations.

Pharmacokinetics

As of the date of the decision to stop enrollment, sample collection for PK analysis is stopped.

For all participants in Cohort 1 and Cohort 2, blood samples will be collected in the main study at Cycle 1/Day 1, Cycle 1/Day 15, Cycle 2/Day 1, Cycle 4/Day 1, and Cycle 8/Day 1, as specified in Table 7 for sparse PK sampling to characterize niraparib exposure in participants with breast cancer and to explore the relationship between exposure to niraparib and responses in efficacy and safety.

A subset of participants in Cohort 1 will have additional blood samples collected in a PK substudy. The PK substudy will include at least the first 40 randomized participants receiving endocrine therapy at sites participating in the PK substudy. The samples collected in the PK substudy will be analyzed to characterize the steady-state PK of endocrine therapy and to assess any potential effect of niraparib on endocrine therapy exposure, as data permit. Based on the randomized nature of the study, it is assumed that approximately 20 participants in the PK substudy will be receiving endocrine therapy with niraparib, while the remaining participants will be receiving endocrine therapy with placebo, allowing for a comparison of endocrine therapy PK with or without niraparib co-administration. Additional participants may be included in the PK substudy if there are too few participants receiving any of the individual endocrine therapies to meet the objectives of the substudy; if feasible, 6 participants per endocrine therapy will be targeted.

In the PK substudy, participants will have blood samples collected at Cycle 1/Day 15, as specified in Table 8, at which time niraparib exposure will have reached steady state.

Brief Summary

The purpose of this study is to assess the efficacy and safety of niraparib in participants with either t*BRCA*mut HER2− breast cancer (including TNBC) or t*BRCA*wt TNBC with molecular detectable disease based on the presence of ctDNA following surgery or completion of adjuvant therapy. The study was originally designed as double-blind. As of the date of the decision to stop the study, the study was centrally unblinded.

Study details include the following:

As of the date of the decision to stop enrollment, the study will conclude when the last participant has completed their last study procedure (as outlined in Section 1.3). Study duration details outlined below are no longer applicable.

- Study duration:

- Treatment duration: Participants may continue study treatment until disease recurrence, death, withdrawal of consent, loss to follow-up, or until unacceptable toxicity. Those participants who have completed 39 cycles (approximately 3 years) with no evidence of recurrence will have the option to either continue treatment or stop treatment at that time (see Section 6.7). Participants on niraparib may continue treatment under Protocol Amendment 03 per protocol if they are considered by the Investigator to be deriving benefit.
- Visit frequency: Weekly for Cycles 1 and 2 (participants have the option of local laboratory/clinic and/or at-home nursing visits for Cycle 1/Days 1 (postdose), 8, 15, and 22 and Cycle 2/Days 1 (postdose), 8, 15, and 22) and every 4 weeks thereafter; EOT Visit within 7 days after last dose; Safety Follow-up Visit 30 (+7) days after last dose; and Post-treatment Follow-up with assessments every 90 (±14) days for 2 years after the last dose and every 180 (±14) days thereafter. **See Section 1.3 for updated visits/frequencies as of the date of the decision to stop enrollment and Table 12 under Protocol Amendment 04**.

Number of Participants

Per the original study design, the number of participants was the following:

- Cohort 1: A total of approximately 200 participants will be randomized.
- Cohort 2: A total of approximately 600 participants will be randomized.

A total of 40 participants were randomized in the study.

Treatment Groups and Duration

Following a confirmed detectable ctDNA test result, participants will be randomized 1:1 to receive either niraparib or placebo and dosed with treatment.

Niraparib will be supplied as CCI [redacted]. Placebo will be provided as CCI [redacted] The starting dose will be based upon the participant's hepatic function and baseline body weight and/or baseline platelet count.

Participants with normal or mildly impaired hepatic function (as defined in Section 4.3 of the full protocol) and a baseline body weight ≥77 kg and baseline platelet count ≥150,000/μL will be administered a niraparib starting dose of 300 mg orally once daily. Participants with normal or mildly impaired hepatic function and a baseline body weight <77 kg or baseline platelet count <150,000/μL will be administered a niraparib starting dose of 200 mg orally once daily. Participants with moderate hepatic impairment (defined as total bilirubin >1.5× and ≤3×upper limit of normal (ULN) and any level of aspartate aminotransferase elevation) will be administered a niraparib starting dose of 200 mg orally once daily, regardless of baseline body weight or baseline platelet count. Participants with severe hepatic impairment are excluded.

Niraparib and placebo treatment will be blinded. **As of date of the decision to stop enrollment, the study was centrally unblinded. For participant management, under Protocol Amendment 04, refer to Table 12. Prior to implementation of PACT, refer to Section 1.3, and once the PACT Phase begins, refer to Section 6.7.**

Note: All SAEs assessed as related by the Investigator continue to be reported for all study participants until study close out and all AEs of special interest (AESIs), regardless of causality, continue to be reported for all study participants until death or loss to follow up.

Participant Selection Criteria

Enrollment of new participants is permanently stopped due to Sponsor decision.

Prescreening

To qualify for Prescreening, participants must meet the following criteria:

P1. Histologically confirmed Stage I to III non-metastatic primary invasive breast cancer that is one of the 2 following phenotypes:

a. TNBC defined as:

- Estrogen receptor (ER) and progesterone receptor (PgR) negative, defined as IHC nuclear staining <1%, and
- HER2– defined as follows:

- IHC 0, 1+ without ISH, or
- IHC 2+ and ISH non-amplified as defined by 2018 ASCO-CAP guidelines [Wolff, 2018]

b. ER and/or PgR positive, HER2– breast cancer defined as follows:

- ER and/or PgR positive defined as IHC nuclear staining ≥1%, and
- HER2– defined as:
  - IHC 0, 1+ without ISH, or
  - IHC 2+ and ISH non-amplified as defined by 2018 ASCO-CAP guidelines [Wolff, 2018]

Participants with multifocal tumors are eligible provided that all lesions are within the same quadrant and have similar ER, PgR, and HER2 staining. Multicentric and synchronous bilateral breast cancers are not allowed.

For participants who received neoadjuvant therapy and have discordant ER, PgR, and/or HER2 receptor results between the diagnostic biopsy (pretreatment) and surgical pathology (post neoadjuvant therapy), the receptor status of the pretreatment specimen determines eligibility. If the biopsy and the surgical specimens are discrepant in the adjuvant setting (i.e., participants had initial surgery), results from the surgical specimen define HR status. Those participants determined to be TNBC based on the pretreatment specimen should not subsequently receive tamoxifen or an aromatase inhibitor as part of their breast cancer treatment.

Note: ER and PgR may be graded using the Allred scoring system, where TNBC is defined to be 0 out of 8 or 2 out of 8,or staining in <1% of cancer cells and HR+ is defined to be a score of ≥3 out of 8.

P2. **New participants joining the study (i.e., have not previously provided Prescreening consent prior to Protocol Amendment 02)** must meet the following criteria:

a. <u>For participants who underwent initial surgery (Adjuvant approach):</u>

- TNBC participants must meet at least 1 of the following criteria:
  - Node-positive (≥pN1, any tumor size), or
  - Node-negative (pN0) or axillary node micro-metastasis (pN1mi) with invasive primary tumor ≥15 mm
- HR+ participants must meet at least 1 of the following criteria:
  - Node-positive with ≥4 involved nodes (≥pN2, any tumor size), or
  - Node-negative (pN0) or axillary node micro-metastasis (pN1mi) with invasive primary tumor >5 cm (≥pT3), or

- Either node-positive with 1 to 3 involved nodes (pN1) OR node-negative or axillary node micro-metastasis with invasive primary tumor >2 cm but ≤5 cm (pT2N0 or pT2N1mic). Invasive tumor must also meet 1 of the following:
  - Grade 3
  - Grade 1 or 2 with ER+/PgR-
  - Grade 1 or 2 with ER-/PgR+

b. <u>For participants who underwent neoadjuvant chemotherapy followed by surgery (Neoadjuvant approach):</u>

- All participants must have shown a definitive response to preoperative chemotherapy by pathological, radiological, or clinical evaluation (see Appendix 1)
- TNBC participants must have residual invasive breast cancer in the breast and/or resected lymph nodes (non-pCR) (any grade is allowed)
- HR+ participants must have residual invasive breast cancer in the breast and/or resected lymph nodes (non-pCR), AND meet 1 of the following criteria:
  - Node-positive prior to or after neoadjuvant treatment (≥cN1 or ≥pN1, any tumor size)
  - Invasive primary tumor size >2 cm prior to or after neoadjuvant treatment (≥cT2 or ≥pT2)

c. **<u>For HR+ participants who underwent neoadjuvant endocrine-only therapy followed by surgery (Neoadjuvant approach, but without any preoperative chemotherapy)</u>**

- All participants must have shown a definitive response to preoperative endocrine therapy by pathological, radiological, or clinical evaluation (see Appendix 1)
- HR+ participants must have residual invasive breast cancer in the breast and/or resected lymph nodes (non-pCR), AND meet 1 of the following criteria:
  - Node-positive with ≥4 involved nodes (≥pN2, any tumor size), or
  - Node-negative (pN0) or axillary node micro-metastasis (pN1mi) with invasive primary tumor >5 cm (≥pT3), or
  - Either node-positive with 1 to 3 involved nodes (pN1) OR node-negative or axillary node micro-metastasis with invasive primary tumor >2 cm but ≤5 cm (pT2N0 or pT2N1mic). Invasive tumor must also meet 1 of the following:
    - Grade 3

- Grade 1 or 2 with ER+/PgR-
- Grade 1 or 2 with ER-/PgR+

Participants who previously completed Prescreening under previous versions of the protocol and who are deemed to have been Prescreen failures due to negative ctDNA testing results on all allotted tests may re-enter Prescreening provided they are eligible to continue Prescreening testing as per protocol (see criterion P4) AND meet all staging criteria as defined above in criterion P2 a to c.

Participants who are currently participating in ongoing Prescreening at the time of Protocol Amendment 02 consent, and who are eligible to continue Prescreening testing as per protocol (see criterion P4), must have Stage I to III non-metastatic primary invasive breast cancer as per criterion P1, but are not required to meet staging criteria as defined in criterion P2 a to c. As of the date of the decision to stop enrollment, participants who were deemed prescreen failures under previous versions of the protocol will not be reconsented and will not return for any prescreening procedures.

P3. HR+ breast cancer participants must have a documented mutation in *BRCA1* or *BRCA2* that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) identified through local testing.

P4. Signed prescreening consent.
New participants joining the study (i.e., have not previously provided Prescreening consent prior to Amendment 02) must sign consent within the following timepoints:

a. **For TNBC participants (t*BRCAwt* or t*BRCA* unknown)**: TNBC participants who have not been tested for t*BRCA* or have no mutation identified (t*BRCA*wt) must sign prescreening consent no later than within 12 weeks from the end of definitive therapy.

- NOTE: Participants receiving pembrolizumab must also consent to Prescreening within 12 weeks of completing definitive therapy (i.e., curative-intent surgery, chemotherapy, and/or radiation, whichever happens last). Pembrolizumab is NOT included in the definition of definitive therapy in this protocol, and participants may continue to receive pembrolizumab as per standard of care during the study, with ctDNA testing performed according to the schedule outlined in Table 2 (footnote a).

b. **For known t*BRCAmut* TNBC or HR+ breast cancer participants:** Participants who have a known and documented deleterious **or** suspected deleterious t*BRCA* mutation identified through local testing must sign prescreening consent no later than 5 years from end of definitive therapy (the first ctDNA test is recommended as soon as they are eligible after completing their last definitive therapy).

Participants who are currently participating in ongoing Prescreening at the time of implementation of Protocol Amendment 02, or who completed Prescreening in the past under previous versions of the protocol, must provide Prescreening

consent for additional ctDNA testing as per Protocol Amendment 02, but are not required to meet the consent timepoint windows as described in criterion P4 a to b.

Participants who are eligible to either re-enter Prescreening or to continue ongoing Prescreening ctDNA testing are those who continue to meet other prescreening eligibility criteria and meet 1 of the following criteria at the time of consent for Protocol Amendment 02:

- Participant is currently participating in ongoing Prescreening at the time of Protocol Amendment 02 implementation, has at least 1 additional ctDNA test left per the original testing schedule, and has not been deemed a Prescreen failure
- Participant previously completed Prescreening under previous versions of the protocol and was deemed to have Prescreen-failed due to negative ctDNA testing results on all allotted tests, AND still remains within the defined testing duration window from end of definitive treatment at the time of reconsent:
    - Participants with TNBC (t*BRCA*wt or t*BRCA* unknown) may resume ctDNA testing so long as no more than 24 months has elapsed since the end of definitive treatment.
    - Participants with known t*BRCA*mut (either TNBC or HR+) may resume ctDNA testing so long as no more than 6 years has elapsed since the end of definitive treatment.

Additional ctDNA testing for participants eligible to resume or continue Prescreening testing will occur according to the schedule outlined in Table 13, Table 14, and Figure 3. As of the date of the decision to stop enrollment, prior prescreen-fail patients (who had not already signed Protocol Amendment 02 consent), are not allowed to be re-enrolled or reconsented and no further assessments or ctDNA testing are allowed.

P5. Completed prior standard therapy for curative intent, including all of the following, if indicated: neoadjuvant treatment, surgery, adjuvant radiotherapy, and adjuvant chemotherapy. Participants with HR+HER2− t*BRCA*mut breast cancer may be receiving concurrent adjuvant endocrine therapy. Participants with TNBC may receive concurrent adjuvant pembrolizumab, if clinically indicated. All participants may receive concurrent bisphosphonates or denosumab. Participants are allowed and encouraged to enter Prescreening as soon as possible per protocol, and may be eligible to start the Prescreening process prior to the completion of adjuvant therapy (see Figure 1 , Table 2, and details of permitted concomitant medications outlined in Section 6.8).

P6 An archival tumor tissue specimen of the primary tumor sufficient in quality and quantity for ctDNA assay design and t*BRCA* and HRD testing is required. As of the date of the decision to stop enrollment, no further t*BRCA* and HRD testing will be performed (see Section 1.3).

NOTE: If the participant has a prior history of additional primary breast cancers, which appear eligible for prescreening in this ZEST trial (see exclusion criterion 12),

the lesion considered at highest risk for recurrence based on the investigator's discretion will be used for ctDNA assay design.

P7. Have a significant risk of disease recurrence as assessed by the Investigator.

P8. Have no known or suspected locally recurrent or metastatic disease as assessed by the Investigator.

P9. Have no known nonmodifiable conflicts with other inclusion and exclusion criteria listed in Section 5.1 and Section 5.2 of the full protocol, respectively.

Screening for Inclusion in Cohort 1 and 2

To be eligible for inclusion in Cohorts 1 and 2 of the study, participants must meet the prescreening criteria outlined above and in Section 5, as well as inclusion criteria outlined in Section 5.1, including, but not limited to, the following

- Stage I to III breast cancer as outlined in Prescreening Criteria
- Completed prior standard therapy for curative intent, including all of the following, if indicated: neoadjuvant treatment, surgery, adjuvant radiotherapy, and adjuvant chemotherapy. Participants with HR+HER2− t*BRCA*mut breast cancer may be receiving concurrent adjuvant endocrine therapy. Participants with TNBC may receive concurrent adjuvant pembrolizumab, if clinically indicated. All participants may receive concurrent bisphosphonates or denosumab (see Figure 1 , Table 2, and details of permitted concomitant medications outlined in Section 6.8).
- Participants with HR+ breast cancer must be on a stable regimen of endocrine therapy, if indicated, for at least 3 months prior to randomization. Ovarian suppression, if indicated, must also have been started at least 3 months prior to randomization.
- Participants must have detectable ctDNA as measured by central Signatera testing (refer to Table 2 for the timing of ctDNA testing).

  An archival tumor tissue specimen of the primary tumor sufficient in quality and quantity for ctDNA assay design and t*BRCA* and HRD is required. (See Prescreening criterion P6 for additional details.)

Participants will be excluded from Cohorts 1 and 2 of the study if the following exclusion criteria are met, including, but not limited to (refer to Section 5.2 of the protocol for full listing of all exclusion criteria):

- Current treatment with a CDK4/6 inhibitor or endocrine therapy other than anastrozole, letrozole, exemestane, and tamoxifen, with or without ovarian suppression.
- Participants have any sign of metastasis or local recurrence after comprehensive assessment conducted per protocol.
- Participants have shown no definitive response to preoperative chemotherapy by pathologic, radiological, or clinical evaluation, in cases where preoperative chemotherapy was administered (see Appendix 1).

Independent Data Monitoring Committee

As of the date of the decision to stop enrollment, an unblinded assessment by an IDMC is no longer needed due to the study being centrally unblinded.

The IDMC will consist of 3 individuals, including 1 biostatistician and 2 physicians who are independent from the Sponsor. The membership, the key responsibilities of the IDMC, and the corresponding procedures will be defined in an IDMC Charter.

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[redacted]

Planned Statistical Analyses

As a result of the decision to stop enrollment into the study, specific assessments such as collection of survival follow-up data, subsequent treatments, patient-reported outcome (PRO) data, etc. will no longer be required (as outlined in Section 1.3).

A final data cut-off (DCO) date represents the end of data collection for the planned final analyses as described in the statistical analysis plan (SAP). A final DCO date will be reached once t**he last participant consents to Protocol Amendment 04 (or withdraws) or meets any protocol-defined stopping criteria (Section 7) and the study will transition to PACT.** Once the final DCO date has been reached, the clinical study database will be closed to new data.

Safety and tolerability of niraparib are being assessed as the primary endpoint and will use the Safety Population. There is no formal hypothesis testing framework being implemented in this study. Estimands are not applicable for the primary endpoint.

Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the SAP and final study report.

1.2. Schema

The ctDNA Prescreening process is described in the flow chart in Figure 1 . Participants are allowed, and encouraged, to start the Prescreening process (including consent and ctDNA assay design) as soon as possible in the postoperative setting, prior to the completion of adjuvant therapy.

The overall study schema is presented in Figure 2. The ctDNA testing schedule is described in Figure 3.

CCI

[redacted]

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[redacted]

Figure 2: Study Schema

Key Eligibility Criteria

- Stage I to III breast cancer with surgical resection of the primary tumor that is confirmed to be either t*BRCA*mut HER2-negative (including HR+ and TNBC) (Cohort 1) or t*BRCA*wt TNBC (Cohort 2)
- ctDNA detected by Signatera (central testing)
- Sufficient archival tissue for eligibility prescreening is required
- Prior adjuvant therapy allowed
- No sign of radiological disease recurrence
- Prior exposure to checkpoint inhibitor allowed ***
- Patients who show no definitive treatment response to pre-operative chemotherapy excluded

Randomization Stratification Factors

Both Cohorts

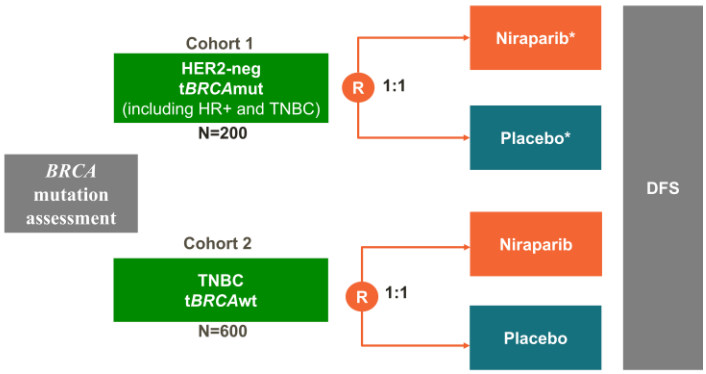
- Time post last intervention**:<6m vs ≥6m
- Prognostic stage of breast cancer (Stage I/II vs Stage III)

Cohort 1

- HR status: positive (HR+) vs negative (TNBC)

Cohort 2

- Prior use of adjuvant capecitabine (yes vs no)



* HR+ participants in Cohort 1 will receive background endocrine therapy (anastrozole, letrozole, exemestane, and tamoxifen, with or without ovarian function suppressing agents).
** Time of last intervention is defined as the date of most recent oncological surgery, date of last adjuvant chemotherapy, or date of last radiotherapy fraction, whichever occurred later.
*** Participants with TNBC may receive concurrent adjuvant pembrolizumab, if clinically indicated.
Abbreviations: *BRCA*=breast cancer susceptibility gene; ctDNA=circulating tumor DNA; DFS=disease-free survival; HER2=human epidermal growth factor receptor 2; HR=hormone receptor, R=randomization; t*BRCA*mut=tumor *BRCA* mutation (somatic or germline); t*BRCA*wt=tumor *BRCA* wild-type; TNBC=triple-negative breast cancer.
As of 25 April 2023, study enrollment has been permanently stopped due to Sponsor decision. Participants will no longer be randomized, and the study was centrally unblinded.

Upon Protocol Amendment 04 implementation at all sites, once the last participant consents to Protocol Amendment 04 (or withdraws) or meets any protocol-defined stopping criteria (Section 7), the study will transition to PACT.

CCI

[redacted]

CCI

1.3. Schedule of Activities

The SOA for Prescreening is provided in Table 2. Prior to Prescreening, participants must meet the Prescreening criteria in Section 5 and have no known conflicts with the other inclusion and exclusion criteria listed in Section 5.1 and Section 5.2 of the full protocol, respectively.

The SOA from the Screening Period to the end of the study is presented in Table 3; each treatment cycle is 4 weeks (28 days). The PK sampling schedule in the main study for all participants is presented in Table 7, and the PK sampling schedule for participants in the PK substudy is presented in Table 8.

As a result of the date of the decision to permanently stop enrollment, no new patients are to be prescreened and/or screened onto the study. Participants in Prescreening can no longer enter screening and any participants in Screening can no longer be randomized. Participants randomized to treatment on the ZEST study may discontinue treatment and be offered scans above standard of care, while some previously specified assessments are now discontinued. Participants should be monitored under Protocol Amendment 03 as follows (also outlined in Table 11)

- For participants Prescreening and ctDNA-negative as of the date of the decision to stop enrollment, see Table 4 for monitoring assessments.
- For participants that are ctDNA+ as of the date of the decision to stop enrollment, but not yet randomized onto the study (includes participants in either Prescreening or Screening that are ctDNA+), see Table 5.
- For those participants randomized in the ZEST study as of the date of the decision to stop enrollment, see Table 6.
- All PK sampling is to be stopped.

PACT Phase:

Participants who continue to receive study treatment (niraparib) during the PACT Phase will be monitored and receive follow-up care in accordance with standard local clinical practice. Safety assessments will revert to the standard of care at a participant's particular study site. SAEs, AESIs, AEs leading to discontinuation of study treatment, overdose and pregnancy reports will continue to be reported directly to the Sponsor via paper forms (or alternative reporting method as indicated by Sponsor, should one become available) through 30 days after the last dose of study treatment (see Section 10.9, Section 10.10, and Section 10.11). Participants receiving surveillance scans (as per Table 12) will continue to be offered scans above standard of care until stopping criteria are met (Section 7). For participants discontinuing treatment in the PACT Phase, an EOT Visit is not required.

Table 2 Schedule of Activities – Prescreening

Visit: Procedure:	Prescreening	Notes
Informed consent for prescreening	X	A Prescreening informed consent specific to ctDNA testing will be issued ahead of the main informed consent. For new study participants, prescreening informed consent will be obtained no later than 5 years since the end of definitive therapy for TNBC or HR+ HER2- breast cancer patients with known and documented t*BRCA* mutation determined locally; for TNBC patients with unknown t*BRCA* status or t*BRCA*wt status, prescreening consent will be obtained no later than 12 weeks since the end of definitive therapy (after surgery if adjuvant treatment is not indicated or after adjuvant treatment). Note: In both cases, prescreening ICF may be obtained post-operatively and/or during adjuvant chemotherapy or radiation treatment. For prior participants who are resuming or continuing ctDNA testing, please see Prescreening criteria P2 and P4 for eligibility and consent details, and Table 13 and Table 14. As of the date of the decision to stop enrollment, prescreening of new patients on the study is discontinued unless outlined in Table 4 and Table 5 for ongoing participants. To continue in the study under Protocol Amendment 03, existing participants will be reconsented as outlined in Table 4 and/or Table 5. **To continue in the study under Protocol Amendment 04, existing participants will be reconsented. See Table 12 for participant management under Protocol Amendment 04.**
Eligibility	X	As of the date of the decision to stop enrollment, prescreening of new patients on the study is discontinued unless outlined in Table 4 and Table 5 for ongoing participants.
Demography	X	As of the date of the decision to stop enrollment, prescreening of new patients on the study is discontinued unless outlined in Table 4 and Table 5 for ongoing participants.
Disease characteristics	X	Tumor characteristics to be collected include, but are not limited to, histologic tumor type, tumor grade, tumor stage (clinical prognostic, pathologic prognostic, and/or anatomic staging) as per AJCC 8th edition; (see Section 8.2.1/Appendix 13), and response to neoadjuvant chemotherapy (as applicable). Primary pathology reports will be collected from biopsy and all surgical resections characterizing ER status (with percent or Allred score if available), PgR (with percent or Allred score, if available), and HER2 status (with IHC ISH, if available), as well as tumor grade. If the participant's disease recurs during prescreening, scans/recurrence response/new tumor information will also be collected. As of the date of the decision to stop enrollment, prescreening of new patients on the study is discontinued unless outlined in Table 4 and Table 5 for ongoing participants.

Visit: **Procedure:**	**Prescreening**	**Notes**
Anticancer, radiation therapies, and surgical procedures for current indication, including date of end of definitive therapy, prior to Screening	X	Includes cancer-related information, including medical, surgical, cancer (including genotyping), medication history, and end of definitive therapy date. Information about current or prior interventions should specifically be collected (as applicable): bisphosphonate/denosumab use, and PD-1/PD-L1 inhibitor use, ipsilateral breast/axillary surgery, contralateral breast/axillary surgery, and/or salpingo-oophorectomy. Note: End of definitive therapy is defined as the date of completing curative-intent surgery, adjuvant chemotherapy and/or adjuvant radiation, whichever happens last. Pembrolizumab is NOT included in the definition of definitive therapy in this protocol. As of the date of the decision to stop enrollment, prescreening of new patients on the study is discontinued unless outlined in Table 4 and Table 5 for ongoing participants.
Tumor tissue for ctDNA assay design, *BRCA* status testing, and HRD testing	X	Tumor tissue sample from primary tumor. Tumor tissue will be obtained either after the participant's last intervention (after surgery if adjuvant treatment is not indicated or after adjuvant treatment) or during adjuvant chemotherapy or radiation treatment. As of the date of the decision to stop enrollment, testing of new patients will be discontinued; however, *BRCA* results from testing already in progress (i.e., testing started prior to 25 April 2023) will be shared, per protocol.
Pathology report submitted	X	Pathology reports will be submitted either after the participant's last intervention (after surgery if adjuvant treatment is not indicated or after adjuvant treatment) or during adjuvant chemotherapy or radiation treatment. The report will accompany samples sent for testing. As of the date of the decision to stop enrollment, this assessment is discontinued for new patients; however, for any participant in prescreening at the time of the amendment, these may have already been submitted.
Blood sample for WES testing (for ctDNA assay design)	X	Blood sample for ctDNA assay design (WES testing) will be obtained either after surgery if adjuvant treatment is not indicated or during/after chemotherapy or radiation adjuvant treatment. The sample may also be used for genetics and translational research (see Section 8.7 and Section 8.8 for details). As of the date of the decision to stop enrollment, this assessment is discontinued for new patients.

Visit: **Procedure:**	**Prescreening**			**Notes**
Blood sample for ctDNA testing	Initial ctDNA test[a] as soon as the participant is eligible, at least 4 weeks after surgery or as soon as possible after end of adjuvant treatment (see Figure 3). Participants receiving pembrolizumab should follow additional ctDNA assessment schedules outlined in footnote a.	For TNBC with unknown t*BRCA* or t*BRCA*wt status, up to 9 additional tests (10 total tests). For TNBC or HR+ breast cancer with known t*BRCA* mutation determined locally, up to 18 total tests. See Figure 3 and Table 13.	Final ctDNA test	Suggested interval between ctDNA tests is approximately 8 weeks ±2 weeks for the first 6 months from end of definitive therapy and then every 12 weeks thereafter (up to Month 24 since the end of definitive therapy) as outlined in Figure 3 and Table 13. For TNBC or HR+ breast cancer patients with known t*BRCA* mutation, up to 8 more tests may be performed (~1 every 6 months) for up to 6 years (Month 72) from the end of definitive therapy. Initial ctDNA sample (for all new participants in any cohort) should be obtained no later than 4 weeks of signing prescreening consent or as soon as the participant is eligible for testing following end of definitive therapy. For participants with TNBC who are receiving adjuvant pembrolizumab following surgery, the first ctDNA test may occur during adjuvant pembrolizumab treatment provided that all adjuvant radiation and adjuvant chemotherapy have been completed (if indicated; see footnote a for further details). Participants with TNBC on adjuvant pembrolizumab who are found to have detectable ctDNA and who are otherwise eligible for the study will be allowed to start niraparib concurrently with the remaining cycles of adjuvant pembrolizumab. *HR+ participants in Cohort 1 should have started a stable regimen of endocrine therapy at least 6 weeks prior to the initial blood sample for ctDNA testing in order to allow for full study eligibility. In addition, CK4/6 inhibitors, if given, should be completed at least 6 weeks prior to initial blood sample for ctDNA testing. As a result of the date of the decision to permanently stop enrollment, ctDNA testing was adjusted (as outlined in Table 4) for ctDNA-negative participants and discontinued (as outlined in Table 5 for ctDNA+ participants not yet randomized. Prior prescreen-fail patients (who had not already signed Protocol Amendment 02 consent), are not allowed to be re-enrolled or reconsented and no further assessments or ctDNA testing are allowed.
Adverse events	X			Events related to ctDNA and WES blood sample collection procedures

Abbreviations: AJCC=American Joint Committee on Cancer; *BRCA*=breast cancer susceptibility gene; ctDNA=circulating tumor DNA; ER= estrogen receptor; FFPE=formalin-fixed paraffin-embedded; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; HRD=homologous recombination deficiency; IHC=immunohistochemistry; ISH= in situ hybridization; PD-1=programmed death protein 1; PD-L1=programmed cell death ligand 1; PgR=progesterone receptor; t*BRCA*=tumor breast cancer susceptibility gene; WES=whole exome sequencing.
HR+ participants in Cohort 1 need to be on a stable regimen of endocrine therapy, if indicated, for a minimum of 3 months prior to randomization. Ovarian suppression, if indicated, must also have started at least 3 months prior to randomization.

[a] Timing of initial ctDNA test in relation to pembrolizumab use:

1) Initial ctDNA test should occur at least 4 weeks after surgery, after completion of adjuvant treatment with radiation and/or chemotherapy (if indicated), or after at least 12 weeks of pembrolizumab have been given in any setting, whichever happens last.
2) If pembrolizumab is permanently discontinued prior to receiving at least 12 weeks, then the initial ctDNA test should occur at least 4 weeks after surgery, after completion of adjuvant treatment with radiation and/or chemotherapy (if indicated), or after at least 12 weeks from the first dose of pembrolizumab was given in any setting, whichever happens last.

As of the date of the decision to stop enrollment, prescreening of new patients on the study is discontinued. Assessments for currently eligible ongoing participants in Prescreening under Protocol Amendment 03 are outlined in Table 4 and Table 5.

Table 3 Schedule of Activities – Screening Period Through End of Study for All Cohorts

Visit: Cycle:	Screening	Niraparib or Placebo Treatment Period (28-day cycles)										EOT (or ED)	Safety FUP[a]	Post-treatment FUP[b]	Notes
		C1				C2				C3	C(n)				
Day: Procedure:	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
Informed consent	X														A Prescreening informed consent specific to ctDNA testing will be issued ahead of the main informed consent. To continue in the study under Protocol Amendment 03, existing participants will be reconsented as outlined in Table 5 and/or Table 6, as applicable. **To continue in the study under Protocol Amendment 04, existing participants will be reconsented. See Table 12 for participant management.**
Eligibility	X														If a participant recurs during Screening, scans, recurrence response, and new tumor information will be collected.

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
Prior anticancer, radiation therapy, and surgical procedures for historical cancers	X														Includes medical, surgical, cancer (including genotyping), and medication history. Information (as applicable) about current or prior interventions should specifically be collected: bisphosphonate/denosumab use, PD-1/PD-L1 inhibitor use, ipsilateral breast/axillary surgery, contralateral breast/axillary surgery, and/or salpingo-oophorectomy.
Medical history	X														Includes medical and cancer history (including genotyping), as well as family history.
Substance use history	X														As of the date of the decision to stop enrollment, discontinued for ctDNA+ participants not yet randomized (see Table 5 for assessments).

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
Treatment assignment (randomization)		X													As of the date of the decision to stop enrollment, randomization is discontinued. For participants that are ctDNA+ and not yet randomized at the time of the amendment see Table 5 for participant management.
12-lead ECG	X														ECG does not need to be repeated if patient requires rescreening. As of the date of the decision to stop enrollment, ECGs are discontinued for ctDNA+ participants not yet randomized (see Table 5 for assessments).
ECOG performance	X	X				X				X	X	X			As of the date of the decision to stop enrollment, ECOG assessment is discontinued for participants on

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
status															placebo, and for ctDNA+ participants not yet randomized (see Table 5 for ctDNA+ participants).
Physical examination	X	X				X				X	X		X		Full physical examination should be performed at the time of Screening. Symptom-directed physical examinations may be performed thereafter. As of the date of the decision to stop enrollment, assessments are discontinued for participants on placebo, and for ctDNA+ participants not yet randomized (see Table 5 for ctDNA+ participants).

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
Height	X														Height is not required after the Screening assessment. As of the date of the decision to stop enrollment, this is discontinued for ctDNA+ participants not yet randomized (see Table 5).
Temperature, weight, and respiration rate	X	X				X				X	X	X	X		Respiratory rate is required at Screening, and thereafter only if clinically indicated. As of the date of the decision to stop enrollment, assessment is discontinued for participants on placebo, and for ctDNA+ participants not yet randomized (see Table 5 for ctDNA+ participants).

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
Blood pressure and heart rate monitoring	X	X*	X*	X*	X*	X*	X*	X*	X*	X	X	X	X		*Must be monitored weekly for the first 2 cycles (8 weeks), then on Day 1 of each subsequent cycle. If unable to attend the clinic visits, BP and heart rate (pulse) must be monitored at home-nursing visits or at a local laboratory/clinic for visits outlined in Section 4.1 and Section 8.4.3 on the dates of these visits (recommended after remaining seated for 5 to 10 minutes). Three readings of BP and heart rate are also recommended as outlined in Section 8.4.3. As of the date of the decision to stop enrollment, this assessment is discontinued for all participants on placebo. This assessment is discontinued at Screening

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
															for ctDNA+ participants not yet randomized (see Table 5).
AE monitoring and review	Reporting of safety events is to begin at the time of ctDNA Prescreening ICF signature date only for events related to ctDNA and WES blood sample collection procedures. All AEs and SAEs are required to be captured from the signing of the main study ICF through 30 days after the last dose of study treatment or start of new anticancer therapy; whichever occurs first. SAEs assessed by the Investigator as related to study treatment**, are to be collected until study closeout** and all AESIs, regardless of causality, are to be collected until **death or loss to follow up** Any pregnancies in WOCBP participating in the study that occur within 180 days post-treatment discontinuation are to be captured.														For France, see Section 10.14.1.1 for pregnancy reporting requirements.
Concomitant		X	X	X	X	X	X	X	X	X	X	X	X		Details regarding collection of endocrine therapy,

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
medication review															ovarian suppression, bisphosphonate/denosumab treatment, and pembrolizumab are specified in the eCRF completion guidelines. As of the date of the decision to stop enrollment, this assessment is discontinued for participants on placebo.

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
Serum or highly sensitive urine pregnancy test (WOCBP only)	X	X				X				X	X	X			Pregnancy testing (serum or highly sensitive urine pregnancy test) must be conducted within 72 hours prior to the first dose of study treatment and then, starting in Cycle 2, within 72 hours of Day 1 of every cycle for the duration of the treatment period. Test result must be available and negative before the first dose of study treatment. Further details regarding pregnancy testing at Screening and during the study are provided in Section 5.1 and Section 8.4.6. Additional pregnancy testing may be necessary if required by local practices or regulations or if potential pregnancy is suspected. As of the date of the decision to stop enrollment, this assessment is discontinued for participants on placebo.

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
HIV, hepatitis B, and hepatitis C screening	X														If participant was tested within 3 months prior to first dose of study treatment, testing at Screening is not required. As of the date of the decision to stop enrollment, this is discontinued for ctDNA+ participants not yet randomized (see Table 5).
Hematology	X	X	X	X	X	X				X	X	X	X		If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC will also be required for an additional 4 weeks after the AE has been resolved to

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
															the specified levels, after which monitoring every 4 weeks may resume. On Cycle 1/Day 8, Cycle 1/Day 15, and Cycle 1/Day 22, samples for CBC can be drawn ± 1 day of the listed visit, as needed. For Cycle 2/Day 1 and Cycle (n)/Day 1, CBC blood draws may be up to 72 hours prior to the visit, as needed. See Appendix 2 for specific parameters to be measured. As of the date of the decision to stop enrollment, this assessment is discontinued for participants on placebo, and discontinued for ctDNA+ participants not yet randomized (see Table 5 for ctDNA+ participants).
Clinical	X	X				X				X	X	X	X		Serum/plasma chemistry parameters that will be

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
chemistry															measured are listed in Appendix 2. Samples for chemistry labs for Cycle 2/Day 1 and Cycle (n)/Day 1 visits may be drawn up to 72 hours prior to the visit, as needed. As of the date of the decision to stop enrollment, this is discontinued for participants on placebo, and for ctDNA+ participants not yet randomized (see Table 5 for ctDNA+ participants).
Urinalysis	X														
Coagulation	X														Specific coagulation factors will be evaluated as presented in Appendix 2.

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
															As of the date of the decision to stop enrollment, this is discontinued for ctDNA+ participants not yet randomized (see Table 5).

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
Blood sample for ctDNA testing	Please see Table 2 for ctDNA testing schedule for Prescreening	X	Every 12 weeks (84±7 days) from randomization until disease recurrence. ctDNA screening should continue every 12 weeks if the participant stops treatment for any reason other than disease recurrence per RECIST v1.1, death, withdrawal of consent, or loss to follow-up.									X			Sample will be collected prior to niraparib administration on Cycle 1/Day 1. During the Treatment Period, samples will be collected every 12 weeks from randomization until disease recurrence. As of the date of the decision to stop enrollment, ctDNA testing is discontinued for all participants.
Blood sample for [redacted]		X								X		At time of disease recurrence			Blood sample at Cycle 1/Day 1, at Cycle 3/Day 1, and at time of disease recurrence [redacted]

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
Optional tumor tissue sample upon disease recurrence												At time of disease recurrence prior to subsequent anticancer therapy			For exploratory analyses, submission of a fresh frozen tumor tissue specimen at time of disease recurrence is highly encouraged. Biopsy must be performed prior to initiation of subsequent anticancer therapy but does not need to occur within 7-days of last dose. As of the date of the decision to stop enrollment, this sample collection is discontinued for all participants.
Blood samples for PK in main study	See Table 7. As of the date of the decision to stop enrollment, collection of blood samples for PK is discontinued for all participants.														
Blood samples	See Table 8. As of the date of the decision to stop enrollment, collection of blood samples for PK is discontinued for all participants.														

Visit: **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended that the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
for PK substudy															
PRO collection: EORTC-QLQ-C30, EQ-5D-3L, FACT-GP5, PGIS/PGIC, and a subset of items from the PRO-CTCAE		X				X				X	X	X	X	First 2 Post-treatment Follow-up assessments	PROs should be completed on the assigned clinic visit day prior to any clinical procedures (see Section 8.9). PGIC only will be collected starting on Cycle 2/Day 1 and every 28 days thereafter. As of the date of the decision to stop enrollment, PRO collection is discontinued for all participants.

Visit: / **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ± 3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
CT or MRI for DFS assessment	X For CT or MRI falling out of 6 weeks prior to first dose window, consult the medical monitor.	Every 12 weeks (84±7 days) from date of randomization for the first 2 years (Year 1 Weeks 12, 24, 36, 48; Year 2, Weeks 60, 72, 84, 96) and every 24 weeks (168±7 days) thereafter, or more frequently as clinically indicated (unscheduled), until Investigator assessment of disease recurrence using RECIST v1.1. Imaging should continue according to the specified window interval if the participant stops treatment for any reason other than disease recurrence per RECIST v1.1, death, withdrawal of consent, or loss to follow-up.													IV contrast-enhanced CT scan of the chest, abdomen, and pelvis; IV contrast-enhanced MRI of the abdomen and pelvis plus noncontrast CT of the chest should only be conducted if IV contrast-enhanced CT cannot be performed (eg, if participant is sensitive to IV CT contrast or contrast shortage). If MRI is performed at Baseline, it should be preferentially continued throughout the study. PET imaging is allowed if needed; refer to Appendix 3 for specific guidelines for use. The same imaging and anatomical coverage should be used throughout the study. If brain metastasis is suspected, IV contrast-enhanced MRI is preferred over IV contrast-enhanced CT for imaging of the brain. It is important to adhere to the imaging schedule. If scans are performed outside of the specified window interval and the participant has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. If an equivocal new lesion is observed on a postbaseline radiological assessment, a follow-up scan should be acquired at least 4 weeks later to reassess. On the follow-up scan, if the equivocal new lesion becomes unequivocal, the date of progression is the date of the scan when the new lesion first appeared (refer to Appendix 3). Any lesion assessed by the Investigator as representative of metastatic disease should be biopsied, if possible, to document disease recurrence histologically. All radiological images/scans, scheduled and unscheduled, must be submitted (preferably electronically) to a central imaging vendor for QC, storage, and analysis by BICR**.** As of the date of the decision to stop enrollment, scans are not to be submitted to a central imaging vendor. BICR analysis is no longer applicable.

Visit:	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
Cycle:		**C1**				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ± 3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
Bone scan	X	Bone scans performed between randomization and disease recurrence only if clinically indicated.													Baseline bone scan will be performed within 42 days (6 weeks) of randomization. Bone scans do not need to be repeated if patient requires rescreening.
Niraparib or placebo dispensed/ collected		X				X				X	X				Missed doses will also be recorded as outlined in Section 6.4.1. If there is a change in weight from Screening to C1D1 to above or below the 77 kg threshold for dosing, then dosing of study drug should be based on weight from C1D1 As a result of the date of the decision to stop enrollment, the study was centrally unblinded and participants on placebo must immediately discontinue treatment. Placebo dispensation is also discontinued. For participants continuing on niraparib, see Table 6.

Visit: / **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT (or ED)**	**Safety FUP[a]**	**Post-treatment FUP[b]**	**Notes**
		C1				**C2**				**C3**	**C(n)**				
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (+7) days after last dose**	**Every 90 (±14) days for 2 years after last dose and then every 180 (±14) days**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments completed within 7 days of the first dose do not need to be repeated. It is recommended the Screening Period start within 14 days of confirmed detectable ctDNA (i.e., ctDNA+ status), provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (except as noted for specific assessments in this SOA) are required to be repeated if they fall outside of 6 weeks prior to first dose. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ± 3 days and weekly visits within ± 1 business day (relative to C1D1). As of the date of the decision to stop enrollment, randomization is stopped. Discontinued assessments are outlined in the table below and monitoring of participants previously randomized is outlined in Table 6.
Anticancer therapy following study treatment													X	X	Anticancer therapy includes systemic therapy, radiation therapy, or surgical intervention. If new anticancer treatment is started before the Safety Follow-up Visit, it must be collected during this visit as outlined in the eCRF completion guidelines. As of the date of the decision to stop enrollment, this is discontinued for all participants.
Disease progression on next anticancer therapy assessment														X	As of the date of the decision to stop enrollment, this is discontinued for all participants.
Follow-up status (survival assessment)														X	Survival status may be collected outside the protocol window on request, as per Section 4.1. As of the date of the decision to stop enrollment, this is discontinued for all participants.

Abbreviations: AE=adverse event; AESI=AE of special interest; BICR=blinded independent central review; BMx=biomarker; BP=blood pressure; *BRCA*=breast cancer susceptibility gene; C=cycle; CBC=complete blood count; CRF=case report form; CT=computed tomography; ctDNA=circulating tumor DNA; ctDNA+=ctDNA -positive; D=day; ECG=electrocardiogram;

ECOG=Eastern Cooperative Oncology Group; ED=early discontinuation/withdrawal; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module; EOT=End of Treatment; EQ-5D-3L=EuroQoL 5-dimensional questionnaire 3-level version; FACT-GP5=Functional Assessment of Cancer Therapy-General Population; FUP=Follow-up Period; HER2=human epidermal growth factor receptor 2; HIV=human immunodeficiency virus; ICF=informed consent form; IV=intravenous; MRI=magnetic resonance imaging; n=number of subsequent cycle; PD-1=programmed death protein 1; PD-L1=programmed cell death ligand 1; PET=positron emission tomography; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PK=pharmacokinetics; PRO=patient-reported outcome; PRO-CTCAE=Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; QC=quality control; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; SOA=Schedule of Activities; WES=whole exome sequencing; WOCBP=women of childbearing potential.

a. As of the date of the decision to stop enrollment, the entire Safety FU Visit, and all associated assessments, are discontinued for participants on placebo at the time of unblinding. For participants on niraparib continuing on the study, see Table 6 or assessments.
b. As of the date of the decision to stop enrollment, the entire Post-treatment FU Visit, and all associated assessments, are discontinued for all participants.

Table 4 Schedule of Activities: Prescreening for Participants Not Yet ctDNA-positive (i.e., ctDNA-negative) Under Protocol Amendment 03

Visit: / Procedure:	Prescreening/Monitoring	Notes Assessments outlined in this table should be collected and/or continue as part of Prescreening for ctDNA-negative participants already in Prescreening as of the date of the decision to stop enrollment.
Informed consent for prescreening	X	As of the date of the decision to stop enrollment, no new participants will be enrolled. Participants remaining on study must be reconsented under Protocol Amendment 03 with a new ICF. **Participants remaining on study must be reconsented under Protocol Amendment 04**.
Eligibility	X	Confirmation of eligibility to continue. As of the date of the decision to stop enrollment, no new participants will be enrolled.
Demography	X	
Disease characteristics	X	Tumor characteristics to be collected as outlined in Table 2.
Anticancer, radiation therapies, and surgical procedures for current indication, including date of end of definitive therapy, prior to Screening	X	As outlined in Table 2.
Blood sample for WES testing (for ctDNA assay design)	X	As outlined in Table 2. Samples prepared for Q2 are no longer required.
Blood sample for ctDNA testing	For Participants in Prescreening as of the date of the decision to stop enrollment and <12 months from end of definitive therapy: up to 2 additional ctDNA tests (excluding initial ctDNA test) until they reach 12 months from end of definitive therapy **or final DCO is reached, whichever comes first**. The frequency of these 2 additional tests is at the discretion of the Investigator.	As a result of the decision to stop enrollment, ctDNA-negative participants currently in Prescreening who are more than 12-months from end of definitive therapy as of the date of the decision to stop enrollment (25 April 2023) should have no further testing. Prior prescreen-fail patients (those that failed under previous versions of the protocol but who had not already signed Protocol Amendment 02 consent), are not allowed to be re-enrolled or reconsented and no further assessments or ctDNA testing are allowed. Samples prepared for Q2 are no longer required.
Adverse events	X	Events related to ctDNA and WES blood sample collection procedures should be reported as outlined in Section 8.5.
CT or MRI scan	X	For participants who were ctDNA-negative as of the date of the decision to stop enrollment, but subsequently test ctDNA+, participants will be offered 1 scan for staging purposes.

Visit: **Procedure:**	**Prescreening/Monitoring**	**Notes** Assessments outlined in this table should be collected and/or continue as part of Prescreening for ctDNA-negative participants already in Prescreening as of the date of the decision to stop enrollment.
Bone Scans	X	ctDNA-negative participants who were ctDNA-negative as of the date of the decision to stop enrollment, but subsequently test ctDNA+, participants will be offered 1 scan for staging purposes

Table 5 Schedule of Activities Prescreening/Screening For Participants Currently ctDNA-positive and Not Yet Randomized as of Protocol Amendment 03

Visit Procedure:	Assessment	Notes ctDNA+ participants must have had a positive test as of the date of the decision to stop enrollment (25 April 2023). If testing was started prior to the date of the decision was made to stop enrollment and the result is obtained after the date of the decision to stop enrollment, and was positive, the participant will be considered part of the ctDNA+ population and currently monitored accordingly.
Prescreening		Participants that are ctDNA+ in Prescreening on the date of the decision to stop enrollment should have completed collection of all Prescreening assessments outlined in this table. Participants in Prescreening but who have not proceeded to Screening as of the date of decision to stop enrollment should not proceed to Screening but can continue with Protocol Amendment 03 Monitoring Assessments if they consent to do so.
Informed consent for prescreening	X	As outlined in Table 2.
Eligibility	X	Confirmation of eligibility to continue.
Demography	X	
Disease characteristics	X	As outlined in Table 2.
Anticancer, radiation therapies, and surgical procedures for current indication, including date of end of definitive therapy, prior to Screening	X	As outlined in Table 2.
Tumor tissue for ctDNA assay design, *BRCA* status testing, and HRD testing		As of the date of the decision to stop enrollment, this assessment is discontinued for all participants; however, if *BRCA* testing was already in progress as of the date of the decision to stop enrollment, *BRCA* results will be shared. **Samples prepared for Q2 are no longer required.**
Blood sample for ctDNA testing		As a result of the decision to stop enrollment, no further ctDNA testing should occur for participants who have tested ctDNA+. **Samples prepared for Q2 are no longer required.**
Adverse events	X	Events related to ctDNA and WES blood sample collection procedures
Screening		For ctDNA+ participants in Screening as of the date of the decision to stop enrollment, Prescreening assessments as outlined above should have been completed and collected; Screening assessments outlined in this table should also be completed.
Informed consent	X	As a result of the decision to stop enrollment, participants who wish to continue surveillance scans will need to provide consent under Protocol Amendment 03 by signing a new ICF. **Participants remaining on study and entering PACT Phase must be reconsented under Protocol Amendment 04.**
Eligibility	X	As outlined in Table 3.
Concomitant Medication Review	X	As outlined in Table 3.

Visit **Procedure:**	**Assessment**	**Notes** ctDNA+ participants must have had a positive test as of the date of the decision to stop enrollment (25 April 2023). If testing was started prior to the date of the decision was made to stop enrollment and the result is obtained after the date of the decision to stop enrollment, and was positive, the participant will be considered part of the ctDNA+ population and currently monitored accordingly.
Medical History	X	As outlined in Table 3.
Protocol Amendment 03 Monitoring		For All ctDNA+ participants as of the date of the decision to stop enrollment (regardless of whether in Prescreening or Screening at the time).
CT or MRI for DFS Assessments	At the discretion of the Investigator	All ctDNA+ participants as of the date of the decision to stop enrollment (regardless of whether in Prescreening or Screening at the time), will be offered the option of CT surveillance scans for assessment of disease as frequently as every 12 weeks, or less frequently at the discretion of the Investigator. Scans may continue until progressive disease/disease recurrence or participant withdrawal, in accordance with the judgment of the Investigator.
Bone Scans	At the discretion of the Investigator	Bone scans will only be performed if clinically indicated.

Table 6 Schedule of Activities – For Previously Randomized Participants Continuing Under Protocol Amendment 03 and Protocol Amendment 04 Prior to the Data Cut-off and Transition to PACT Phase

As of the date of the decision to stop enrollment, all study treatment must be stopped for participants on placebo at the time of unblinding. Participants that were on placebo will be monitored for AEs and participants may remain on study to continue scans until disease progression or participant withdrawal, as outlined for participants on niraparib in the table below. Participants will be required to sign an ICF under Protocol Amendment 03 prior to continuing scans.

Visit:	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT**	**Safety FUP**	**Notes**
Cycle:		**C1**				**C2**				**C3**	**C(n)**			
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days decision to discontinue**	**30 (+7) days after last dose**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments outlined in this table should have been collected as part of Screening for these ctDNA+ participants already randomized at the time of the decision to stop enrollment. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1).
Informed consent	X													A Prescreening informed consent specific to ctDNA testing will have been issued ahead of the main informed consent. For participants who wish to remain on study, they must be reconsented under Protocol Amendment 03. **Participants remaining on study and entering PACT Phase must be reconsented under Protocol Amendment 04.**
Eligibility	X													As outlined in Table 3.
Prior anticancer, radiation therapy, and surgical procedures for historical cancers	X													As outlined in Table 3.
Medical history	X													As outlined in Table 3.

Visit:	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT**	**Safety FUP**	**Notes**
Cycle:		**C1**				**C2**				**C3**	**C(n)**			
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days decision to discontinue**	**30 (+7) days after last dose**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments outlined in this table should have been collected as part of Screening for these ctDNA+ participants already randomized at the time of the decision to stop enrollment. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1).
Substance use history	X													
12-lead ECG	X													
ECOG performance status	X	X				X				X	X	X	X	
Physical examination	X	X				X				X	X		X	As outlined in Table 3.
Height	X													Height is not required after the Screening assessment.
Temperature, weight, and respiration rate	X	X				X				X	X	X	X	
Blood pressure and heart rate monitoring	X	X*	X*	X*	X*	X*	X*	X*	X*	X	X	X	X	*Must be monitored weekly for the first 2 cycles (8 weeks), then on Day 1 of each subsequent cycle. Three readings of BP and heart rate are also recommended as outlined in Section 8.4.3.

Visit:	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT**	**Safety FUP**	**Notes**
Cycle:		**C1**				**C2**				**C3**	**C(n)**			
Day: **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days decision to discontinue**	**30 (+7) days after last dose**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments outlined in this table should have been collected as part of Screening for these ctDNA+ participants already randomized at the time of the decision to stop enrollment. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1).
AE monitoring and review	Reporting of safety events is to begin at the time of ctDNA Prescreening ICF signature date only for events related to ctDNA and WES blood sample collection procedures. **All AEs and SAEs are required to be captured from the signing of the main study ICF through 30 days after the last dose of study treatment or start of new anticancer therapy; whichever occurs first. SAEs assessed by the Investigator as related to study treatment are to be collected until study closeout and all AESIs, regardless of causality, are to be collected until death or loss to follow up.** Any pregnancies in WOCBP participating in the study that occur within 180 days post-treatment discontinuation are to be captured.													For France, see Section 10.14.1.1 for pregnancy reporting requirements.
Concomitant medication review		X	X	X	X	X	X	X	X	X	X	X	X	As outlined in Table 3.
Serum or highly sensitive urine pregnancy test (WOCBP only)	X	X				X				X	X	X		As outlined in Table 3.
HIV, hepatitis B, and hepatitis C screening	X													As outlined in Table 3.
Hematology	X	X	X	X	X	X				X	X	X	X	As outlined in Table 3.
Clinical chemistry	X	X				X				X	X	X	X	As outlined in Table 3.

Visit: / **Cycle:**	**Screening**	**Niraparib or Placebo Treatment Period (28-day cycles)**										**EOT**	**Safety FUP**	**Notes**
		C1				**C2**				**C3**	**C(n)**			
Day: / **Procedure:**	**Up to 6 weeks before D1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**Within 7 days decision to discontinue**	**30 (+7) days after last dose**	All tests and procedures are required to be performed, and results evaluated, prior to dosing. Screening assessments outlined in this table should have been collected as part of Screening for these ctDNA+ participants already randomized at the time of the decision to stop enrollment. Treatment cycles are 28 (±3) days long. Monthly visits should occur within ±3 days and weekly visits within ± 1 business day (relative to C1D1).
Urinalysis	X													
Coagulation	X													
CT or MRI for DFS assessment	X For CT or MRI falling out of 6 weeks prior to first dose window, consult the medical monitor	Every 12 weeks (84±7 days) from date of randomization for the first 2 years (Year 1 Weeks 12, 24, 36, 48; Year 2, Weeks 60, 72, 84, 96) and every 24 weeks (168±7 days) thereafter, or more frequently as clinically indicated (unscheduled), until Investigator assessment of disease recurrence using RECIST v1.1. Imaging should continue according to the specified window interval if the participant stops treatment for any reason other than disease recurrence per RECIST v1.1, death, withdrawal of consent, or loss to follow-up. As of the date of the decision to stop enrollment, participants on niraparib or placebo at the time of unblinding may continue scans per protocol, or less frequently at the discretion of the Investigator, until disease progression.											As outlined in Table 3. Note, as of the date of the decision to stop enrollment, scans are not to be submitted to a central imaging vendor. BICR analysis is no longer applicable. Note: scans may continue post-EOT until progressive disease/disease recurrence or participant withdraws.
Bone scan	X	Bone scans performed between randomization and disease recurrence only if clinically indicated.												As outlined in Table 3
Niraparib dispensed/ collected		X				X				X	X			As outlined in Table 3.

Table 7 PK Sampling Schedule for All Participants (Discontinued Under Protocol Amendment 03)

Visit: **Cycle:**	**Niraparib or Placebo Treatment Period (28-day cycles)**								**Notes**
	C1				**C2**	**C3**	**C4**	**C8**	**As a result of Protocol Amendment 03, no further PK sampling will be performed**.
Day: **Procedure:**	**1**	**8**	**15**	**22**	**1**	**1**	**1**	**1**	
Blood samples for niraparib PK									Blood samples for PK in the main study will be collected for all participants in Cohort 1 and Cohort 2. If participants are routinely taking their niraparib/placebo dose in the evening, they must be instructed to transition to niraparib/placebo morning dosing 1 week before PK testing.
Predose (Up to 60 minutes prior to dosing)	X		X		X		X	X	Participants will be instructed to hold their dose of study treatment until the predose PK sample has been taken. For Cycle 4/Day 1 and Cycle 8/Day 1 samples, if a participant discontinues treatment before the scheduled blood draw, a blood draw for PK will be done at the EOT Visit.
3 hours postdose (±15 minutes)	X		X		X				Participants will be instructed to hold their dose of study treatment until the predose PK sample has been taken. Three-hour postdose sample is not required on Cycle 1/Day 15 for participants in the PK substudy.

Abbreviations: C=cycle; EOT=End of Treatment; PK=pharmacokinetics.

Table 8 PK Sampling Schedule for Participants in the PK Substudy (Discontinued Under Protocol Amendment 03)

Visit: **Procedure:**	**Cycle 1, Day 15**	**Notes**
Blood samples for PK substudy		The PK substudy will include at least 40 participants receiving endocrine therapy in Cohort 1. Participants in the PK substudy will also have PK samples collected at the time points in Table 7 , with the exception of the 3-hour postdose sample on Cycle 1/Day 15. Participants must be instructed to dose study treatment and endocrine therapy in the morning for 1 and 2 weeks, respectively before PK sampling on Cycle 1/Day 15. **As a result of decision to stop enrollment, no further PK sampling will be performed.**
Predose (Up to 60 minutes prior to dosing)	X	Participants will be instructed to hold their dose of niraparib/placebo and endocrine therapy until the predose PK sample has been taken. Niraparib/placebo must be taken first and the endocrine therapy immediately after (within 5 minutes).
1 hour postdose (±15 minutes)	X	Participants in the PK substudy who vomit after taking their study treatment on a PK sampling day will need to return another time for their PK assessments.
2 hours postdose (±15 minutes)	X	
4 hours postdose (±15 minutes)	X	
6 hours postdose (±15 minutes)	X	
8 hours postdose (±15 minutes)	X	

Abbreviations: PK=pharmacokinetics.

2. INTRODUCTION

As of 25 April 2023, the decision was communicated by the Sponsor that enrollment in the ZEST study was permanently stopped due to feasibility of study completion (i.e., the study was unable to randomize participants in the planned timeframe based on randomization projections as the study had lower-than-expected rates of ctDNA-positivity and a much higher-than-expected proportion of patients with a ctDNA-positive (ctDNA+) test showing radiographically detectable disease during screening assessments). There was no change in the benefit-risk and no safety concerns identified for participants in the study.

2.1. Study Rationale

Study 213831 was designed as a study of niraparib as treatment for participants with tumor breast cancer susceptibility gene mutated (t*BRCA*mut, which includes participants with germline *BRCA*mut [g*BRCA*mut] and/or somatic *BRCA*mut [s*BRCA*mut]) human epidermal growth factor receptor 2-negative (HER2−) breast cancer or tumor *BRCA* wild-type (t*BRCA*wt) triple-negative breast cancer (TNBC) who have molecular disease based on the presence of circulating tumor DNA (ctDNA) levels after completion of definitive treatment, including all of the following, if indicated: neoadjuvant treatment, surgery, adjuvant radiotherapy, and adjuvant chemotherapy; end of definitive therapy is defined as the date of completion of curative-intent surgery, adjuvant chemotherapy, or adjuvant radiotherapy, whichever was last.

For patients with Stage I, II, IIIA, IIIB, or operable IIIC breast cancer, treatment includes surgical removal of the primary tumor, with lymph node dissection as required [Cardoso, 2019; NCCN, 2020]. Although patient survival after surgery can be improved with adjuvant local and systemic therapy, the risk of recurrence in many patients with breast cancer remains high ([Steeg, 2016], reviewed in [Coakley, 2019]). Once definitive therapy is complete, there is no standard of care surveillance or treatment for patients with TNBC, beyond clinical monitoring, until metastatic disease presents. Similarly, for patients with hormone receptor positive (HR+)/HER2− breast cancer on adjuvant endocrine therapy, there is no standard of care surveillance or additional treatment until metastatic disease presents [NCCN, 2021]. Once the disease becomes metastatic, the 5-year survival rates are 11.5% for TNBC and 30.4% for HR+/HER2− breast cancer [SEER, 2019].

Current tumor markers to determine the risk of recurrence after definitive therapy, such as carcinoembryonic antigen, cancer antigen 27-29, and cancer antigen 15-3, lack sensitivity and are typically used only in the metastatic setting [Kokko, 2002; Lumachi, 1999; Mariani, 2009]. To identify the patient population at high-risk of recurrence, current efforts are directed at identification of molecular detectable disease, as measured by the presence of ctDNA. Several studies in multiple cancer types, including breast cancer, have shown that molecular detectable disease can be identified using liquid biopsies by tracking tumor mutations in ctDNA and the presence of ctDNA has been demonstrated to be predictive of clinical or radiological relapse [Coombes,

2019]. Currently, there is no standard of care for patients who have detectable ctDNA following their last intervention (surgery or adjuvant therapy) but who have not yet developed radiologic or clinically evident metastatic disease.

The single-agent efficacy of 2 poly(ADP-ribose) polymerase (PARP) inhibitors, olaparib and talazoparib, has been demonstrated in patients with g*BRCA*mut HER2− breast cancer, including patients with g*BRCA*mut TNBC, in the locally advanced(talazoparib) and metastatic (olaparib and talazoparib) settings [Litton, 2018; Robson, 2017] and in patients with s*BRCA*mut metastatic breast cancer (olaparib) [Tung, 2020].

Studies in TNBC support homologous recombination deficiency (HRD) status as a predictor of response to treatment. HRD testing classifies tumors as either positive for a deficiency in homologous recombination DNA repair (homologous recombination deficient [HRd]) or without a defect in this pathway (homologous recombination proficient [HRp]). In patients with TNBC, including g*BRCA*wt TNBC, HRd disease is frequent [Chopra, 2020] and has been associated with improved response to anticancer treatment [Sharma, 2018; Staaf, 2019; Telli, 2016; Zhao, 2017]. Efficacy of PARP inhibitors has been observed in patients with HRd breast cancer. Patients with early HRd breast cancer treated with neoadjuvant olaparib in combination with paclitaxel had a pathological complete response (pCR) rate of 55.1%, compared with 48.6% in patients treated with paclitaxel/carboplatin [Fasching, 2021]. In patients with HRd metastatic TNBC treated with veliparib plus cisplatin, longer progression-free survival (PFS) was observed compared to treatment with cisplatin alone [Sharma, 2020]. In a study of olaparib in patients with treatment-naïve TNBC, in which 18 of 32 patients obtained an objective response (56.3%), HRd TNBC was associated with response; 16 of 18 responders (88.9%) had homologous recombination mutations and/or *BRCA* methylation compared with 4 of 14 nonresponders (28.6%) [Eikesdal, 2020]. In a study of neoadjuvant rucaparib in patients with untreated localized TNBC, 70% of whom had HRd cancers, HRDetect-high status was associated with ctDNA suppression [Chopra, 2020].

Clinical activity of niraparib as neoadjuvant treatment in t*BRCA*mut HER2− breast cancer has been demonstrated [Han, 2019]. Additionally, niraparib has demonstrated antitumor efficacy in ovarian cancer beyond *BRCA*mut disease. Results from prior niraparib studies in ovarian cancer indicate a consistent continuum of clinical benefit across biomarker-defined subpopulations and that the benefit of niraparib treatment extends beyond patients with *BRCA*mut disease [Gonzalez-Martin, 2019; Mirza, 2016; Moore, 2019].

Based on these findings, Study 213831 will assess niraparib in participants with t*BRCA*mut HER2− breast cancer (including TNBC) or t*BRCA*wt TNBC who have molecular detectable disease, as determined by the presence of detectable ctDNA, until participants relapse with locally recurrent or metastatic disease. Given the substantial prevalence of HRd disease in TNBC and the expected particular sensitivity to PARP inhibition in these patients [Chopra, 2020], HRD status will be assessed in tumor tissue of t*BRCA*wt TNBC participants, and the primary efficacy analysis in t*BRCA*wt TNBC participants will be based on the HRd subpopulation, followed by testing of the overall cohort of t*BRCA*wt TNBC participants (see Section 9). As of the date of the decision to stop enrollment, this is no longer applicable.

2.2. Background

2.2.1. Overview of Breast Cancer

Breast cancer is the most common cancer in women globally and makes up approximately 15% to 24% of all new cancer cases in women [Bray, 2018; SEER, 2019]. The incidence of breast cancer in men is approximately 70- to 100-fold lower than the incidence in women [American Cancer Society, 2020]. According to GLOBOCAN, the estimated number of new cases worldwide in women and men combined was 2,088,849 in 2018 [Bray, 2018]. In the European Union-28, the estimated number of new cases in women that year was 404,920 [Cardoso, 2019].

There are 4 main breast cancer subtypes characterized by the expression status of hormone receptor (HR) status (estrogen receptor [ER] and progesterone receptor [PgR]), and the lack or presence of overexpression of the human epidermal growth factor 2 (HER2):

- HR positive, HER2 negative (HR+/HER2−)
- HR negative, HER2 negative (HR−/HER2−; “triple-negative”)
- HR positive, HER2 positive (HR+/HER2+)
- HR negative, HER2 positive (HR−/HER2+)

Studies show that the prevalence of the 4 main breast cancer subtypes is dependent on factors such as sex, age, and ethnicity. Male breast cancer is almost always HR+, and HER2 expression is uncommon [Cardoso, 2018a].

African American women are more likely to have TNBC with the highest prevalence in premenopausal African American women. These ethnic or menopausal differences are not seen in either the estrogen receptor positive (ER+)/HER2+ breast cancer subgroup or the ER+/HER2− subgroup [Carey, 2006].

For approximately 5% to 10% of patients with breast cancer, the breast cancer is hereditary [Baretta, 2016]. Up to 25% of hereditary breast cancers have been linked to specific germline mutations, with mutations in *BRCA1* and *BRCA2* making up approximately 20% [Balmana, 2011; Shiovitz, 2015]. *BRCA*mut breast cancer is characterized by a more aggressive phenotype than sporadic breast cancer: *BRCA*mut breast cancer is often of higher histological grade and is frequently triple-negative [Antoniou, 2003; Armes, 1998; Southey, 2011]. Although the prevalence of t*BRCA*mut in TNBC varies depending on factors such as age, ethnicity, and region, based on data from The Cancer Genome Atlas, the prevalence of t*BRCA*mut in TNBC is up to 25% [Belli, 2019].

Survival and recurrence are dependent on tumor stage and tumor subtype, as follows:

- Patients with metastatic TNBC have a 5-year survival rate of only 11.5%; 30.4% for patients with metastatic HR+/HER2− breast cancer; 36.8% for patients with metastatic HR−/HER2+ breast cancer; and 43.5% for patients with metastatic HR+/HER2+ breast cancer [SEER, 2019].

- Patients with early stage TNBC have a very high 5-year recurrence rate (30% to 50%) compared to patients with other breast cancer subtypes [Azim, 2020; Dent, 2007].
- Patients with TNBC demonstrate a peak in the risk of recurrence 1 to 3 years after last intervention, while the risk of recurrence in patients with other types of breast cancer, including HR+/HER2− breast cancer, seems to be steady for at least 15 years [Dent, 2007].
- Patients with TNBC have a higher risk of distant recurrence than those with other breast cancer subtypes [Dent, 2007].
- Peak of recurrence is 12 months postsurgery in patients with TNBC and 36 months postsurgery in patients with HR+/HER2− breast cancer [Park, 2012].

The population selected for this study are participants with TNBC (HER2−/HR−) and HR+/HER2− breast cancer. Treatment of HER2+ breast cancer has evolved such that targeted therapies are the backbone for treatment in both the neoadjuvant/adjuvant and metastatic setting, regardless of *BRCA* status. There are also limited data on the use of PARP inhibitors and their effectiveness in *BRCA*mut HER2+ patients, and available data suggest that the proportion of patients with *BRCA*mut amongst patients with HER2+ breast cancer is low (1.5% to 3.3%) [Hu, 2020; Lang, 2017; Zhong, 2016]. Thus, patients with HER2+ breast cancer have been excluded from this study.

2.2.2. Treatment Options for Patients with Operable HER2− Breast Cancer

Treatment of patients with Stage I, II, IIIA, IIIB, or operable IIIC breast cancer includes surgical removal of the primary tumor, with lymph node dissection as required [Cardoso, 2019; NCCN, 2020]. Surgery may be preceded by neoadjuvant therapy, particularly in patients with locally advanced disease, to reduce tumor size and improve the probability of achieving pCR [Cardoso, 2018b]. For HER2− breast cancer, including TNBC, doxorubicin/cyclophosphamide followed by paclitaxel or docetaxel/cyclophosphamide is the preferred neoadjuvant/adjuvant therapy. Paclitaxel/carboplatin or docetaxel/carboplatin may be used in select patients with operable TNBC [NCCN, 2020]. Addition of platinum can be considered in patients with TNBC or *BRCA*mut breast cancer [Cardoso, 2019].

In order to prevent recurrence and/or metastasis, surgery is often followed by adjuvant chemotherapy or radiation. For HR+/HER2− breast cancer, adjuvant endocrine therapy such as tamoxifen or an aromatase inhibitor is recommended worldwide [NCCN, 2021]; addition of adjuvant chemotherapy is only recommended for patients with high-risk disease [Cardoso, 2019; NCCN, 2020]. For patients with TNBC and residual disease after neoadjuvant therapy with taxane-, alkylator-, and anthracycline-based chemotherapy, capecitabine is recommended [Cardoso, 2019; NCCN, 2020]. Use of capecitabine in this patient population was shown to decrease mortality, although the 5-year mortality rate remains >20% [Masuda, 2017].

Based on the recent OlympiA study (NCT2032823; [Tutt, 2021]), the NCCN guidelines now also recommend the use of 1 year of adjuvant olaparib for high risk, Stage II to III

g*BRCA*mut HER2− breast cancer after completion of adjuvant chemotherapy [NCCN, 2021].

Most recently, pembrolizumab received United States (US) FDA approval for neoadjuvant and adjuvant treatment in patients with TNBC based on results of the Phase 3 KEYNOTE-522 study, a randomized, placebo-controlled study in patients with untreated Stage II or Stage III TNBC that was newly diagnosed or previously untreated. Participants received pembrolizumab or placebo in combination with chemotherapy as neoadjuvant treatment. A pCR rate of 63% (95% CI: 59.5, 66.4) was reported for the pembrolizumab group compared with 56% (95% CI: 50.6, 60.6) in the placebo group. An event-free survival (EFS) event was reported in 123 (16%) participants in the pembrolizumab group and 93 (24%) in the placebo group (hazard ratio = 0.63; 95% confidence interval [CI]: 0.48, 0.82; p=0.00031) [Keytruda USPI, 2021].

2.2.3. HRD Status in TNBC

In studies of TNBC, regardless of *BRCA* status, the percentage of patients with HRd tumors as assessed by CCI [redacted] has been observed to range from 59% to 71% [Chopra, 2020; Mayer, 2020; Sharma, 2018; Staaf, 2019; Telli, 2018].

HRd, based on the CCI [redacted], was associated with improved PFS in metastatic/recurrent TNBC patients treated with veliparib plus cisplatin versus cisplatin alone (hazard ratio=0.53 [95% CI: 0.31, 0.89], *p*=0.016) [Sharma, 2020]. Patients with HRd tumors had improved disease-free survival (DFS) compared to patients with HRp tumors in TNBC patients treated with adjuvant chemotherapy (hazard ratio=0.72 [95% CI: 0.51, 1.00], *p*=0.049), including in t*BRCA*wt patients (hazard ratio=0.64 [95% CI: 0.43, 0.94], *p*=0.023) [Sharma, 2018]. HRd was also associated with pCR following neoadjuvant platinum-based chemotherapy in TNBC [Telli, 2018]. However, in other studies, no association has been observed between CCI [redacted] status and response to platinum-based chemotherapy in patients with TNBC [Mayer, 2020; Tutt, 2018].

The presence of HRd tumors as determined by HRDetect (HRDetect-high status) was associated with improvement in invasive disease-free survival (IDFS) (hazard ratio=0.42 [95% CI: 0.2, 0.87]) and distant relapse-free interval (hazard ratio=0.31 [95% CI: 0.13, 0.76]) in patients with TNBC treated with adjuvant chemotherapy [Staaf, 2019] and was associated with extended median overall survival (OS; *p*=0.04) and total duration of therapy (*p*=0.00029) in patients with advanced breast cancer treated with platinum-based chemotherapy [Zhao, 2017]. In a study of neoadjuvant rucaparib in untreated localized TNBC, HRDetect-high status was associated with ctDNA suppression [Chopra, 2020].

Additionally, HRd tumors were associated with response in patients with treatment-naïve TNBC who were treated with olaparib as neoadjuvant treatment. Of 32 participants with TNBC, 18 had objective response (56.3%), while 16 of 18 responders (88.9%) had homologous recombination mutations and/or *BRCA* methylation compared with 4 of 14 nonresponders (28.6%) [Eikesdal, 2020].

The collective evidence supports HRd disease as a predictor of response to treatment in *BRCA*wt TNBC.

2.2.4. PARP Inhibitors

DNA repair is accomplished by several mechanisms in healthy cells, including but not limited to homologous recombination repair (HRR), nonhomologous end-joining (NHEJ), and base excision repair (BER). Some cells are incapable of HRR due to the inactivation of genes such as *BRCA1* or *BRCA2*. In the absence of HRR, these cells must rely on alternative DNA repair mechanisms.

PARP1 and PARP2 are zinc-finger DNA-binding proteins that detect damaged DNA and promote DNA repair by several mechanisms. For example, after detecting DNA damage, PARP activates the BER pathway via an intracellular signaling mechanism. Conversely, PARP inhibitors block DNA repair by the BER pathway. In cells incapable of HRR (eg, *BRCA1* and *BRCA2* mutations), PARP inhibition leads to irreparable double-strand DNA breaks, collapsed replication forks, and an increased use of the NHEJ pathway. These disruptions result in genomic instability and, ultimately, cell death. The synergy between cellular defect and drug-induced effect is referred to as synthetic lethality [Kaelin, 2005]. Treatment with PARP inhibitors represents an opportunity to selectively kill cancer cells with deficiencies in HRR and other DNA repair mechanisms.

The rationale for employing PARP inhibitors to selectively eliminate cancer cells is supported by data derived from nonclinical ex vivo and in vivo experiments that demonstrate that PARP inhibitors are more potent cytotoxicity inducers in tumors with homozygous inactivation of *BRCA1* or *BRCA2* than in *BRCA*-replete counterparts.

The single-agent efficacy of 2 PARP inhibitors, olaparib and talazoparib, has been shown in 2 separate Phase 3 randomized controlled studies in patients with g*BRCA*mut HER2− breast cancer who had received ≤3 prior lines of chemotherapy. Olaparib received approval for patients with g*BRCA*mut HER2− metastatic breast cancer based on the results of the OlympiAD study, and talazoparib received approval for the treatment of patients with g*BRCA*mut HER2− locally advanced or metastatic breast cancer based on the results of the EMBRACA study. In both studies, PFS was significantly longer in the PARP inhibitor group than in the standard therapy group (OlympiAD study: 7.0 months in the olaparib group versus 4.2 months in the standard therapy group; hazard ratio for disease progression or death=0.58 [95% CI: 0.43, 0.80], $p<0.001$; EMBRACA study: 8.6 months in the talazoparib group versus 5.6 months in the standard therapy group; hazard ratio for disease progression or death=0.54 [95% CI: 0.41, 0.71], $p<0.0001$) [Litton, 2018; Robson, 2017]. The OlympiA trial also recently demonstrated that 1 year of adjuvant olaparib improved IDFS in patients with high-risk Stage II to III *gBRCA*mut HER2− breast cancer [Tutt, 2021]. A significant increase in IDFS was reported in with olaparib compared with placebo with a difference of 8.8% (95% CI: 4.5, 13.0; hazard ratio for invasive disease or death = 0.58; 99.5% CI: 0.41, 0.82; p<0.001). The results of the OlympiA trial provide a practice-changing advancement for the adjuvant treatment of g*BRCA*mut patients with high-risk breast cancer; however, there are many patients for whom the OlympiA results do not apply, including, but not limited to the following:

- Those who achieved pCR;
- TNBC patients who received adjuvant therapy and who have T1 and/or node-negative disease;

- HR+HER2− patients who received adjuvant therapy and have either node-negative disease or positive nodal disease with involvement of 1 to 3 nodes;
- Those patients who already completed definitive therapy in the past and fall outside the traditional adjuvant 12-week window defined by OlympiA; and
- Those with a s*BRCA*mut.

Additionally, as noted in Section 2.2.3, evidence of efficacy for PARP inhibitors in HRd TNBC has been observed [Chopra, 2020; Eikesdal, 2020; Sharma, 2020].

2.2.5. Niraparib

Niraparib is an orally available, potent, highly selective PARP-1 and -2 inhibitor that is dosed once daily.

Niraparib is approved in multiple countries worldwide including the US, European Union, Switzerland, Australia, Canada, and Saudi Arabia as maintenance therapy for women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete response (CR) or partial response (PR) to platinum-based chemotherapy. **ZEJULA (niraparib) is approved for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to first-line platinum-based chemotherapy. ZEJULA is also approved for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.** CCI [redacted]

2.2.5.1. Efficacy of Niraparib in Maintenance Therapy Following Platinum-based Chemotherapy

The efficacy results in the PRIMA study demonstrated a clinical benefit continuum defined by clinical and molecular biomarkers, with the greatest clinical benefit observed among participants with *BRCA*mut tumors. Furthermore, participants with HRd tumors, regardless of *BRCA* mutation status, had a similar clinical benefit. Median PFS was significantly longer in participants who received niraparib compared to those who received placebo, with correspondingly favorable hazard ratios.

- The study met the primary endpoint in participants with HRd tumors (hazard ratio=0.43 [95% CI: 0.310, 0.588], p<0.0001). Median PFS based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) was 21.9 months in the niraparib arm and 10.4 months in the placebo arm.
- The study met the primary endpoint for the overall population (hazard ratio=0.62 [95% CI: 0.502, 0.755], p<0.0001). Median PFS for participants randomized to niraparib was 13.8 months versus 8.2 months on placebo.
- Participants benefitted from niraparib therapy regardless of tumor HRD test status. Median PFS for participants with HRp tumors randomized to the

niraparib arm was 8.1 months versus 5.4 months in the placebo arm (hazard ratio=0.68 [95% CI: 0.492, 0.944], *p*=0.0203).

- In *BRCA*mut participants, a subset of participants with HRd tumors, treatment with niraparib prolonged median PFS by 11.2 months compared to placebo. Median PFS was 22.1 months in the niraparib arm versus 10.9 months in the placebo arm (hazard ratio=0.40 [95% CI: 0.265, 0.618], *p*<0.0001).
- In the HRd/*BRCA*wt subgroup, treatment with niraparib prolonged median PFS by 11.4 months compared to placebo. Median PFS was 19.6 months in the niraparib arm and 8.2 months in the placebo arm (hazard ratio=0.50 [95% CI: 0.305, 0.831], *p*=0.0064).
- Although immature, OS in the overall population numerically favored niraparib (hazard ratio=0.70 [95% CI: 0.442, 1.106], *p*=0.1238).

The Phase 3 ENGOT-OV16/NOVA study, the first large, randomized study of niraparib, was a double-blind, randomized, placebo-controlled evaluation of participants with platinum-sensitive (defined as achieving a CR or PR and disease progression >6 months after completion of most recent platinum-based therapy) recurrent ovarian cancer. Participants must have received at least 2 platinum-based regimens and had either g*BRCA*mut disease or a tumor with high-grade serous or high-grade predominantly serous histology, but without such g*BRCA*mut (non-g*BRCA*mut). The study was conducted to assess the potential benefit of niraparib treatment in participants with demonstrated platinum responsiveness and aimed to define a molecular biomarker that could bifurcate the participant population into those who benefit from niraparib and those that do not. HRD testing was conducted in the non-g*BRCA*mut cohort to define tumors as either HRd or HRp.

Data from NOVA demonstrated the magnitude of benefit from niraparib maintenance therapy, as measured by the primary endpoint of PFS, when compared with placebo in a platinum-responsive population. Treatment with niraparib significantly prolonged PFS, with the greatest benefit observed among participants with g*BRCA*mut tumors (hazard ratio=0.27), followed by participants with HRd non-g*BRCA*mut tumors (hazard ratio=0.38), and participants with HRp tumors (hazard ratio=0.58). Molecular biomarkers (*BRCA* mutation testing and homologous recombination status) were not useful for identifying a population that had no or little chance of deriving clinically meaningful benefit from niraparib treatment.

In NOVA, the niraparib adverse event (AE) profile was manageable with dose adjustments. A dose modification approach that adjusted each participant to her appropriate dose in the first 3 cycles based on individual tolerance substantially reduced the incidence and severity of treatment-emergent adverse events (TEAEs) in participants, enabling them to continue on a sustained maintenance treatment. Owing to the implementation of this approach, at Cycle 12, of the 163 participants remaining on niraparib treatment in the NOVA study, only 37 (23%) remained on a daily dose of 300 mg, with the remaining participants at either 200 mg (40%) or 100 mg (37%). Because of this, while Grade 3/4 thrombocytopenia was noted in approximately 36% of niraparib-treated participants during Month 1 with dose modifications, the rate of Grade 3/4 thrombocytopenia was less than 1% after Month 3.

In addition to PRIMA and NOVA, niraparib was studied in participants with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with recurrent disease who had received at least 3 prior lines of therapy in QUADRA, a multicenter, open-label, single-arm Phase 2 study. Primary efficacy was determined by evaluation of Investigator-assessed confirmed objective response rate (ORR) as defined by RECIST v1.1 in patient populations with molecular biomarkers (deleterious *BRCA* mutations and other homologous recombination deficiencies) and the clinical biomarker of platinum sensitivity.

The QUADRA study results demonstrated activity of niraparib in late-line participants with ovarian cancer [Moore, 2019]. A confirmed ORR of 24% (95% CI: 16%, 34%) was observed in participants with HRd, platinum-sensitive tumors, with median duration of response (DoR) of 8.3 months (95% CI: 6.5, non-evaluable). QUADRA showed a graduated continuum of clinical activity across a population of participant subgroups defined by clinical and molecular biomarkers, with the greatest activity observed in participants with *BRCA*mut platinum-sensitive tumors (ORR 39%), followed by participants with *BRCA*mut platinum-resistant tumors (ORR 33%) and participants with HRd/non-*BRCA*mut platinum-sensitive tumors (ORR 20%). ORR in participants with *BRCA*mut tumors independent of platinum sensitivity was 29%.

The results from the PRIMA and NOVA studies, supported by the nonclinical data and the activity seen in later lines of treatment, indicate a consistent, durable benefit of niraparib treatment in advanced ovarian cancer patient population regardless of biomarkers.

2.2.5.2. Efficacy of Niraparib in Breast Cancer

Studies evaluating niraparib in participants with breast cancer include Study 3000-01-005 (NEOADJUVANT), Study PR-30-5010-C (BRAVO), and Study 3000-PN162-01-001 (TOPACIO/KEYNOTE-162).

Study 3000-01-005 (NEOADJUVANT) Efficacy Data

Study 3000-01-005 (NEOADJUVANT) was an open-label, single-arm pilot study evaluating the safety and efficacy of niraparib as neoadjuvant therapy in participants with HER2−, t*BRCA*mut (germline or somatic) resectable breast cancer (primary tumor ≥1 cm) who had not received prior treatment for the current malignancy. Participants received niraparib 200 mg orally once daily for 28 days for at least 2 cycles. At the end of 2 cycles, at their treating physician's discretion, participants proceeded directly to surgery, received additional cycles of niraparib (maximum of 6 cycles), or received neoadjuvant chemotherapy.

A total of 21 participants were enrolled and received niraparib [Han, 2019]. As of November 2019, as assessed by magnetic resonance imaging (MRI; primary endpoint), 2 of 21 participants had a best overall response (BOR) of CR, 17 participants had a BOR of PR, and 2 participants had a BOR of stable disease (SD). No participant experienced progressive disease (PD) during the study period. The tumor response rate by MRI, defined as the proportion of participants with a ≥30% reduction in tumor volume from baseline, was 90%. The median decrease in tumor volume by MRI was 86%. These data

show promising antitumor activity in the neoadjuvant treatment of participants with localized HER2−, t*BRCA*mut breast cancer.

Study PR-30-5010-C (BRAVO) Efficacy Data

Study PR-30-5010-C (BRAVO) is an open-label, randomized Phase 3 study in participants with previously treated, HER2−, g*BRCA*mut advanced breast cancer that compared niraparib monotherapy to physician's choice chemotherapy (ie, eribulin, vinorelbine, gemcitabine, or capecitabine). Participants may have received up to 2 prior courses of chemotherapy for advanced breast cancer (not including [neo]adjuvant therapy) or had relapsed within 12 months of adjuvant chemotherapy. Participants with HR+ breast cancer must have received at least 1 line of endocrine therapy and either progressed while receiving this therapy in the metastatic setting or relapsed during or within 1 year of completion of the adjuvant treatment.

A total of 215 participants were randomized 2:1 between niraparib and physician's choice chemotherapy. At the interim analysis, with 105 events of PD or death, recruitment was halted on the basis of futility. A high and imbalanced informative censoring rate was observed in the physician's choice arm in the central review of data (28% physician's choice arm versus 7% niraparib arm). When compared to the niraparib arm, the physician's choice arm had an unusually high rate of discontinuations that occurred prior to the first scan (19% physician's choice arm versus 11% niraparib arm), more participants who were lost to follow-up or never started study treatment (12% physician's choice arm versus 5% niraparib arm), and a greater proportion of ineligible participants (19% physician's choice arm versus 9% niraparib arm). It was concluded that further recruitment would not be productive in generating data that would be interpretable and therefore suitable for registration in this indication.

After enrollment closure, the final analysis was carried out for the primary endpoint, with 135 participants in the niraparib arm and 71 participants in the physician's choice arm. The median follow-up duration was 19.9 months. The median PFS by central review was 4.1 months in the niraparib arm versus 3.1 months in the physician's choice arm (stratified log-rank *p*-value=0.58). The median time to OS was comparable between the niraparib arm and the physician's choice arm (14.5 months versus 15.8 months). The ORR (CR+PR) in the centrally confirmed intent-to-treat (ITT) population with measurable disease based on central review for confirmed and unconfirmed responses was 21.4% and 31.0%, respectively, in the niraparib arm compared with 12.5% and 23.4%, respectively, in the physician's choice arm. The difference between the 2 treatment arms was not statistically significant for either confirmed or unconfirmed response (p=0.3123 and 0.4296, respectively).

Although there was evidence of niraparib's activity in participants with advanced breast cancer and germline mutations in *BRCA1* and *BRCA2*, the high degree of informative censoring in the physician's choice chemotherapy arm prevented the accurate assessment of the study hypothesis that niraparib would be superior to the physician's choice of therapy in this patient population.

Study 3000-PN162-01-001 (TOPACIO/KEYNOTE-162) Efficacy Data

Study 3000-PN162-01-001 (TOPACIO/KEYNOTE-162) is an ongoing, multicenter, open-label, single-arm Phase 1/2 study to evaluate the safety and efficacy of niraparib plus pembrolizumab in enrolled women with advanced or metastatic TNBC or recurrent ovarian carcinoma, irrespective of *BRCA* mutation status. Participants received 200 mg of niraparib orally once daily and 200 mg of pembrolizumab intravenous (IV) on Day 1 of each 21-day cycle.

A total of 55 participants were enrolled in the TNBC cohort in Phase 2 of the study [Vinayak, 2019].

In the full analysis population of this cohort (n=55), 5 participants had a BOR of confirmed CR, 5 had a BOR of confirmed PR, 13 had a BOR of SD, and 24 had a BOR of PD; 8 participants did not have an evaluable postbaseline scan. In the efficacy-evaluable population (n=47), the confirmed ORR was 21% (90% CI: 12%, 33%), and the disease control rate (DCR) was 49% (90% CI: 36%, 62%).

Although the prespecified statistical criterion for the primary objective was not met (null hypothesis of ORR ≤15%), combination treatment with niraparib and an anti-programmed cell death protein 1 (PD-1) antibody provided promising, durable clinical benefit. The median DoR in participants with a confirmed CR or PR had not been reached at the time of data cutoff. The DoR ranged from 4.6 to 15.9 months. Of the 10 participants with confirmed CR or PR, 3 participants had a response duration longer than 1 year, 4 participants had a response duration of 9 to 12 months, and 2 participants had a response duration of 6 to 9 months. Four of the 13 participants with SD continued without disease progression for more than 6 months. The OS data were not mature at the time of the analysis.

In the biomarker-defined evaluable population, 15 of the 47 participants (32%) were t*BRCA*mut, 27 participants (57%) were t*BRCA*wt, and the remaining 5 participants had unknown t*BRCA* status.

The response rate was numerically higher in participants with t*BRCA*mut (n=15, 32%) than in those without confirmed t*BRCA*mut status (n=32, 68%). Among the 15 participants with t*BRCA*mut status, the ORR was 47% (90% CI: 24%, 70%), and the DCR was 80% (90% CI: 56%, 94%). BOR was CR in 2 participants, PR in 5 participants, and SD in 5 participants. Among the 27 participants with t*BRCA*wt status, the ORR was 11% (90% CI: 3%, 26%), and the DCR was 33% (90% CI: 19%, 51%). BOR was CR in 3 participants and SD in 6 participants.

Although clinical activity was more pronounced in participants with t*BRCA*mut disease, the combination treatment demonstrated clinical activity in participants irrespective of *BRCA* mutation status. The ORR of 21% in the efficacy-evaluable population was numerically higher than the single-digit ORRs reported for anti-PD-(L)1 agents in similar patient populations [Adams, 2019; Dirix, 2018; Emens, 2019]. The improvement in response rate did not appear to be driven entirely by stronger activity in the population with t*BRCA*mut because 3 participants with t*BRCA*wt status had CR, and 2 of these 3 participants had no mutation in other HRR pathway genes.

Based on these data, participants on adjuvant pembrolizumab who are found to have detectable ctDNA and are otherwise eligible for the study will be allowed to start niraparib concurrently with the remaining cycles of adjuvant pembrolizumab.

2.2.5.3. Niraparib and Endocrine Therapy

In this study, participants in Cohort 1 with HR+/HER2− breast cancer may receive concomitant endocrine therapy. There is no expectation of a drug-drug interaction for concurrent niraparib and endocrine therapy from either pharmacokinetic (PK) or pharmacodynamic effects. Aromatase is an enzyme that belongs to the cytochrome P450 (CYP) family. Aromatase inhibitors affect estrogen production from androgens by inhibiting the aromatase enzyme activity, which is a part of the estrogen pathway. Because niraparib neither inhibits nor induces any major CYP enzyme, and is not metabolized via this pathway, it is therefore unlikely to diminish effectiveness of aromatase inhibitors.

A PK interaction is also not expected. Endocrine therapies, such as aromatase inhibitors (eg, anastrozole, exemestane, and letrozole) and tamoxifen, are mostly metabolized by CYP enzymes. Because niraparib neither inhibits nor induces any major CYP enzymes, it is unlikely to affect the exposure of endocrine therapies.

2.2.5.4. Niraparib and Pembrolizumab

In this study, participants with TNBC may receive concurrent adjuvant pembrolizumab therapy, as clinically indicated. The combination of niraparib and pembrolizumab has been broadly analyzed in a variety of cancers (see the Niraparib Investigator's Brochure [IB] [GSK Document Number RPS-CLIN-014110]), with examination in breast cancer as outlined in the TOPACIO study (summarized above). No safety concerns have been identified [Konstantinopoulos, 2019; Vinayak; 2019].

2.2.6. Circulating Tumor DNA

Despite improvement in patient survival after surgery with adjuvant and local systemic therapy, the risk of recurrence in many patients with breast cancer remains high ([Steeg, 2016], reviewed in [Coakley, 2019]). The goal of adjuvant therapy is to treat patients who may have micrometastatic disease; however, it is not possible to reliably identify these patients. Thus, many patients receive treatment, often chemotherapy, that they may not need. In order to improve identification of the patient population at high risk of recurrence, current efforts are directed at identification of molecular detectable disease.

Circulating free DNA was detected in the serum of patients with cancer as early as the 1970s [Leon, 1977]. In the 1990s, Sorenson et al confirmed that the circulating free DNA observed in serum from patients with pancreatic adenocarcinoma originated from the tumor (ctDNA) [Sorenson, 1994]. Recent technological advances have demonstrated that the tumor mutational signature is reflected in the ctDNA, and new technologies have been developed to detect the ctDNA using minimally invasive procedures. Analysis of ctDNA in early stage cancer requires the ability to detect very low levels of ctDNA in plasma. Several studies have shown that molecular detectable disease can be identified using liquid biopsies in several cancer types, including breast cancer, by tracking tumor

mutations in ctDNA [Coombes, 2019; Garcia-Murillas, 2019; Garcia-Murillas, 2015; Olsson, 2015]. These studies demonstrated the clinical validity of ctDNA testing.

Clinical Utility of ctDNA

The clinical utility of ctDNA testing is currently being tested in several studies across different tumor types, including the following:

- NRG-GI005 COBRA (NCT04068103) for FOLFOX in colon cancer sponsored by NRG Oncology
- c-TRAK-TN (NCT03145961) for pembrolizumab in TNBC sponsored by the Institute of Cancer Research
- NCT03311958 for nivolumab in diffuse large B-cell lymphoma sponsored by the Fox Chase Cancer Center
- NCT04267237 for RO7198457 + atezolizumab versus atezolizumab in non-small cell lung cancer sponsored by Hoffman-La Roche
- Imvigor010 study (NCT02450331) for atezolizumab as adjuvant monotherapy treatment in muscle invasive urothelial cancer sponsored by Hoffman-La Roche

The presence of ctDNA has been demonstrated to be predictive of clinical or radiological relapse. In a study of 49 participants with primary breast cancer (enrolled after definitive therapy), ctDNA was detected using the Signatera test in 16 participants, all of whom experienced clinical relapse [Coombes, 2019]. The median lead time from ctDNA detection to clinical relapse was 266 days (8.9 months), with 301 days for HR+/HER2− breast cancer and 258 days for TNBC. No ctDNA was detected at any time point in any of the 31 patients who did not experience clinical relapse.

In a study with 55 participants with early stage breast cancer treated with neoadjuvant chemotherapy before surgery, ctDNA was detected in 13 participants, 12 of whom experienced clinical relapse [Garcia-Murillas, 2015]. The median lead time from ctDNA detection to clinical relapse in this study was 7.9 months. No ctDNA was detected in 24 of 25 participants who did not experience clinical relapse. The clinical relevance of ctDNA detection was also demonstrated: Clinical outcomes (including recurrence rate, DFS, and OS) were worse in participants who were ctDNA-positive after surgery than in participants who were ctDNA-negative. DFS was shorter in participants with ctDNA (6.5 months) than in participants without ctDNA (not reached), with a hazard ratio of 25.1.

In addition, a prospective study of 94 patients with advanced solid tumors (including TNBC) treated with pembrolizumab showed that a vast majority of patients with detectable ctDNA at baseline who ultimately achieved clearance of detectable ctDNA had done so after 3 to 12 weeks of immunotherapy treatment [Bratman, 2020]. Those patients with persistent detectable ctDNA after 12 weeks of pembrolizumab were highly unlikely to achieve ctDNA clearance despite additional pembrolizumab treatment.

This new technology therefore provides an opportunity for early detection of tumor molecular recurrence prior to clinical recurrence; introducing therapy at this stage could potentially intercept and reverse disease progression while the disease burden is low, and

the patient has not yet developed radiologically evident metastatic disease. Currently, there is no standard of care for patients who have detectable ctDNA following their last intervention (surgery or adjuvant therapy) but have not yet developed radiologic or clinically evident metastatic disease. GSK therefore believes that the inclusion of participants with t*BRCA*mut HER2− breast cancer (including TNBC) or t*BRCA*wt TNBC who have molecular detectable disease, as determined by the presence of detectable ctDNA in the present study is appropriate and will allow the assessment of niraparib in representative populations with unmet medical need.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of niraparib may be found in the current version of the Niraparib IB [GSK Document Number RPS-CLIN-014110].

2.3.1. Risk Assessment

A summary of risks and mitigations for niraparib is provided in Table 9.

Table 9 Summary of Risks and Mitigations for the Product

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
Thrombocytopenia Anemia Leukopenia Neutropenia Pancytopenia	Based on nonclinical and clinical observations as well as identified risk with PARP inhibitor, niraparib.	Protocol has inclusion criteria that participants must have adequate organ and bone marrow function Protocol provides guidelines for monitoring hematologic laboratory parameters and adverse reactions. Protocol provides Investigator guidance for the clinical management of these events. Protocol provides guidance for dose modification and discontinuation of study treatment.
Hypertension	Cases reported with niraparib.	Protocol includes exclusion criteria for participants who have systolic BP >140 mmHg or diastolic BP >90 mmHg that has not been adequately treated or controlled. Protocol provides monitoring and stopping criteria for discontinuation of study treatment.
Second primary malignancy Myelodysplastic syndrome/Acute myeloid leukemia	Based on nonclinical and clinical observations as well as identified with PARP inhibitor, niraparib.	Protocol provides monitoring and stopping criteria for discontinuation of study treatment.
Embryofetal toxicity	Based on nonclinical and clinical observations as well as identified with PARP inhibitor, niraparib.	Protocol excludes participants who are pregnant or breastfeeding and provides detailed guidance on contraception.
Posterior Reversible Encephalopathy Syndrome (PRES)[a]	Cases reported with niraparib.	Protocol provides monitoring, treatment, including control of hypertension, and stopping criteria for discontinuation of study treatment.

Abbreviation: BP=blood pressure; PARP=poly(adenosine diphosphate-ribose) polymerase.

[a] PRES, a treatable acute neurologic illness characterized by rapid onset headache, visual disturbance, altered consciousness, seizures, hypertension, imaging findings of white matter, parietal and posterior occipital, and vasogenic edema.

2.3.2. Benefit Assessment

Niraparib has demonstrated efficacy in participants with *BRCA*mut ovarian cancer in the NOVA and PRIMA studies, as well as clinical activity in advanced ovarian cancer. The NOVA study (Study PR-30-5011-C) was a Phase 3, double-blind, randomized, placebo-controlled study in participants with platinum-sensitive (defined as achieving a CR or PR and disease progression >6 months after completion of most recent platinum-based therapy) recurrent ovarian cancer. Participants must have received at least 2 platinum-based regimens. Participants had either a g*BRCA*mut or a non-g*BRCA*mut tumor with high-grade serous or high-grade predominantly serous histology. Treatment with niraparib significantly prolonged median PFS compared to treatment with placebo, with the greatest benefit observed among participants with g*BRCA*mut tumors (hazard ratio=0.27 [95% CI: 0.173, 0.410], $p<0.0001$). The treatment effect of niraparib observed in participants with g*BRCA*mut tumors was comparable to that observed in participants

with s*BRCA*mut tumors (subgroup of participants with HRd/non-g*BRCA*mut tumors) (hazard ratio=0.27 [95% CI: 0.081, 0.903], p=0.0248).

Niraparib also showed treatment activity in QUADRA, a Phase 2, multicenter, open-label, single-arm study in participants with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with recurrent disease who had received ≥3 prior lines of therapy (Section 2.2.5.1). In this difficult-to-treat patient population, participants with *BRCA*mut tumors demonstrated an ORR of 29%.

In PRIMA, a Phase 3, double-blind, randomized, placebo-controlled study of niraparib as maintenance treatment in participants with advanced ovarian cancer who were in CR or PR to first-line platinum-based chemotherapy, niraparib showed benefit in participants with HRd tumors (hazard ratio=0.43 [95% CI: 0.310, 0.588], p<0.0001), in the overall population (hazard ratio=0.62 [95% CI: 0.502, 0.755], p<0.0001), and in *BRCA*mut participants (a subset of participants with HRd tumors; hazard ratio=0.40 [95% CI: 0.265, 0.618], p<0.0001).

Preliminary evidence of clinical activity of niraparib in t*BRCA*mut HER2− breast cancer comes from Study 3000-01-005, an open-label, single-arm pilot study evaluating the safety and efficacy of niraparib as neoadjuvant therapy in participants with HER2− t*BRCA*mut resectable breast cancer (primary tumor ≥1 cm) who had not received prior treatment for the current malignancy. A total of 21 participants were enrolled and received niraparib [Han, 2019]. As of November 2019, as assessed by MRI (primary endpoint), 2 of 21 participants had a BOR of CR, 17 participants had a BOR of PR, and 2 participants had a BOR of SD. No participant experienced PD during the study period. The tumor response rate, defined as the proportion of participants with a ≥30% reduction in tumor volume from baseline, by MRI was 90%. The median decrease in tumor volume by MRI was 86%.

Additional information regarding the safety and efficacy data that supported the approval of niraparib for these indications can be found in the current version of the IB and the locally approved product label. The efficacy of PARP inhibitors has also been demonstrated in participants in high risk breast cancers such as HER2− and g*BRCA*mut breast cancer compared with placebo in the OlympiA trial (see Section 2.2.4) with no new safety findings resulting from olaparib treatment [Tutt, 2021].

Additionally, the potential overlapping toxicities between niraparib and anastrozole, letrozole, exemestane, and tamoxifen, with or without ovarian function suppressing agents, include hypertension (anastrozole), nausea, musculoskeletal pain/arthralgia, insomnia, headache, and dyspnea [Arimidex SmPC, 2017; Arimidex USPI, 2019; Aromasin SmPC, 2018; Aromasin USPI, 2019; Femara SmPC, 2019; Femara USPI, 2020; Soltamox SmPC, 2018; Soltamox USPI, 2019; Zejula SmPC, 2020; Zejula USPI, 2020]. There is a low risk of drug-drug interaction for the combination of niraparib and the proposed background endocrine therapies. No interaction is expected at the level of endocrine therapy exposure, as niraparib is not an inhibitor or inducer of the CYP pathways, which drive the elimination of many endocrine agents.

Based on data from studies with niraparib in combination with pembrolizumab [Niraparib, IB], no interaction is expected with exposure for participants taking concurrent adjuvant pembrolizumab. Additionally, initiation of ctDNA prescreening

during adjuvant pembrolizumab and subsequent enrollment for those patients with detectable ctDNA may also be of benefit to patients. As referenced in Section 2.2.6, recent data suggests that if ctDNA has not cleared in patients after 12 weeks of pembrolizumab therapy, then ctDNA is very unlikely to clear at all despite additional treatment with pembrolizumab [Bratman, 2020]. Delaying enrollment onto the trial until after adjuvant pembrolizumab is complete may in turn delay an opportunity for the patient to intervene on expected progressive disease. Therefore, allowing TNBC patients to pursue concurrent pembrolizumab (as clinically indicated) with enrollment onto the trial allows participants earlier access to a potentially effective intervention in a situation where the data suggest potential poor outcome, i.e., with lack of ctDNA clearance after 12 weeks, despite continued immunotherapy.

2.3.3. Overall Benefit/Risk Conclusion

As of communication sent on 25 April 2023, the Sponsor permanently stopped enrollment the ZEST study due to assessment of feasibility to complete the study (i.e., the study was unable to randomize participants in the planned timeframe based on randomization projections as the study had lower-than-expected rates of ctDNA-positivity and a much higher-than-expected proportion of patients with a ctDNA+ test showing radiographically detectable disease during screening assessments) and not due to any safety concerns. There are no changes in the assessment of benefit-risk resulting from this decision.

Niraparib, as a once daily oral treatment, prolonged the effect of platinum-based chemotherapy, substantially improved PFS, and significantly reduced the risk of recurrence or death in a broad ovarian cancer population of patients, thereby enabling a delay in disease recurrence and the need for additional platinum-based or other chemotherapy with its associated cumulative toxicities, as demonstrated in multiple pivotal clinical studies. In addition to the demonstrated efficacy of niraparib in *BRCA*mut ovarian cancer (Section 2.3.2), results from clinical studies indicate a consistent continuum of niraparib treatment across biomarker-defined subpopulations and that the benefit of niraparib treatment extends beyond patients with BRCAmut disease (Section 2.2.5.1).

The AE profile of niraparib consisted of AEs that are commonly managed in the patient population of advanced cancer. The key safety concerns included hematological toxicities, hypertension, and myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and a potential risk of second primary malignancies. Common AEs including Grade 3 and higher AEs were generally manageable with dose modification and clinical treatment, most of which resolved without discontinuation of study treatment.

The benefit/risk profile of niraparib is anticipated to be favorable in the populations in this study with utilization of the risk mitigation strategies as outlined in the study protocol. Allowance of concurrent adjuvant pembrolizumab with niraparib as described in the protocol does not alter the overall benefit/risk assessment.

Based on the observed efficacy of niraparib in ovarian tumors, including *BRCA*mut and *BRCA*wt disease, the preliminary clinical activity of niraparib as neoadjuvant therapy in t*BRCA*mut HER2− breast cancer, and the observed efficacy of other PARP inhibitors in metastatic g*BRCA*mut breast tumors independent of HR status, GSK believes that niraparib will demonstrate efficacy in patients with HER2− breast cancer.

3. OBJECTIVES AND ENDPOINTS AND ESTIMANDS

As of the date of the decision to stop enrollment, safety and tolerability are being assessed as the primary endpoint and will use the Safety (SAF) Population. Estimands are not applicable for the primary endpoint.

Table 10 Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluation of safety and tolerability of niraparib	The incidence of TEAEs, SAEs, and AESIs; TEAEs leading to death, TEAEs leading to dose modifications, and TEAEs leading to discontinuation will be assessed. Clinically relevant laboratory parameters, vital signs, ECOG performance status, and use of concomitant medications will be collected and evaluated as defined in the Statistical Analysis Plan (SAP).
Exploratory	
Evaluation of the efficacy of niraparib relative to placebo as measured by DFS	DFS is defined as the time until disease recurrence, measured from the time of randomization to the earliest date of assessment of disease recurrence or death by any cause, as assessed by Investigator using RECIST v1.1.
Evaluation of distant recurrence-free survival (DRFS)	DRFS is defined as the time from randomization to the first detection of distant metastasis or death by any cause as assessed by Investigator using RECIST v1.1.
Time to first subsequent therapy (TFST)	TFST is defined as the time from randomization to the date of the first anticancer therapy used subsequent to the date of the endpoint DFS or death by any cause.
Time to first subsequent chemotherapy	Time to first subsequent chemotherapy is defined as the time from randomization to the date of the first systemic chemotherapy used subsequent to the date of the endpoint DFS or death by any cause.

Objectives	Endpoints
Time to symptomatic progression	Time to symptomatic progression is defined as the time from randomization to the date of symptomatic progression, which either coincides with or is subsequent to the date of the endpoint DFS. Symptomatic progression includes any of the following: • Development of a skeletal-related event: pathologic fracture, spinal cord compression, or need for surgical intervention or radiation therapy (including palliative radiotherapy) to the bone • Initiation of a new systemic anticancer therapy for cancer pain progression or worsening of disease-related symptoms • Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.
Evaluation of the efficacy of niraparib relative to placebo as measured by invasive disease-free survival (IDFS)	IDFS will be assessed as per definition included in STEEP 2.0 ([Tolaney, 2021] see Section 8.3.7).
Evaluation of the efficacy of niraparib relative to placebo as measured by invasive breast cancer-free survival (IBCFS)	IBCFS will be assessed as per definition included in STEEP 2.0 ([Tolaney, 2021]; see Section 8.3.8)
CCI [redacted]	

Abbreviations: AE=adverse event; ctDNA=circulating tumor DNA; DFS=disease-free survival; DRFS=distant recurrence-free survival; ECOG=Eastern Cooperative Oncology Group; IBCFS=invasive breast cancer-free survival; IDFS=invasive disease-free survival; OS=overall survival; PD=progressive disease; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; SAP=Statistical Analysis Plan; SOA=Schedule(s) of Activities; TEAE=treatment-emergent adverse event; TFST=time to first subsequent therapy; CCI [redacted]

4. STUDY DESIGN

4.1. Overall Design

Study 213831 was designed as a multicenter, multicohort, Phase 3, double-blinded, placebo-controlled study comparing the safety and efficacy of niraparib to placebo in participants who are 18 years and older with either HR+/HER2− t*BRCA*mut breast cancer or TNBC with any *BRCA* mutation status who have detectable ctDNA following completion of definitive therapy, including all of the following, if indicated: neoadjuvant treatment, surgery, adjuvant radiotherapy, and adjuvant chemotherapy; end of definitive therapy is defined as the date of completion of curative-intent surgery, adjuvant chemotherapy, or adjuvant radiotherapy, whichever was last. The study will include 2 separate cohorts: a t*BRCA*mut HER2− breast cancer (including TNBC) cohort (Cohort 1) and a t*BRCA*wt TNBC cohort (Cohort 2).

As a result of assessment of feasibility of study completion (i.e., the study was unable to randomize patients in the planned timeframe based on randomization projections as the study had lower-than-expected rates of ctDNA-positivity and a much higher-than-expected proportion of patients with a ctDNA+ test showing radiographically detectable disease during screening assessments), a decision was made by the Sponsor to permanently stop enrollment into the ZEST study, which was communicated on 25 April 2023 (i.e., the date of the decision to stop enrollment). As of the date of this communication no further randomizations were approved by the Sponsor.

Participants on study as of the date of the decision to discontinue enrollment should be managed under Protocol Amendment 03 as outlined in Table 11.

As of Protocol Amendment 04, participants should be managed as outlined in Table 12. Once the last participant consents to Protocol Amendment 04 (or withdraws) or meets any protocol-defined stopping criteria (Section 7), the study will transition to PACT (see Section 6.7.1 for details).

Data collection for the planned final analysis will end once the final data cut-off (DCO) date is reached. Once the final DCO date has been reached, the clinical study database will be closed to new data. Before the DCO is reached all participants will continue assessments as per SOA Table 4, Table 5, and Table 6.

The end of study is defined in Section 6.7.

Table 11 Summary of Patient Management Under Protocol Amendment 03

	Prescreen fail participants eligible for Prescreening under Protocol Amendment 02	Participants in Prescreening/Screening[a,b]			Randomized Participants[a]	
		Participants <12 months since end of definitive therapy	Participants ≥12 months since end of definitive therapy	Participants ctDNA+ not yet randomized[c]	Participants on niraparib	Participants on placebo
Status Under Protocol Amendment 03	Not eligible to join Protocol Amendment 03	Eligible to continue under Protocol Amendment 03	Not eligible to continue under Protocol Amendment 03	Eligible to continue under Protocol Amendment 03	Eligible to continue under Protocol Amendment 03	Eligible to continue under Protocol Amendment 03
SOA Table	NA	Table 4	NA	Table 5	Table 6	Table 6

a. Participants in Prescreening, Screening, or Randomized as of the date of decision to stop enrollment (25 April 2023)
b. Screening only applies to ctDNA+ participants.
c. If ctDNA testing was started prior to the date of the decision was made to stop enrollment and the result was obtained after the date of the decision to stop enrollment, and was positive, the participant will be considered part of the ctDNA+ population and currently monitored accordingly.

Table 12 Summary of Patient Management Under Protocol Amendment 04

	Participants in Prescreening/Screening[a,b]			Randomized Participants[a]	
	Participants <12 months since end of definitive therapy	Participants ≥12 months since end of definitive therapy	Participants ctDNA+ not yet randomized[c]	Participants on niraparib	Participants on placebo
Status Under Protocol Amendment 04 prior to DCO[d]	Eligible to continue under Protocol Amendment 04 SOA Table 4 with final ctDNA test drawn prior to DCO[d] or participant reaches 12 months since end of definitive therapy, whichever comes first.	Not eligible to continue under Protocol Amendment 04	Eligible to continue under Protocol Amendment 04 as per SOA Table 5 until DCO[d]	Eligible to continue under Protocol Amendment 04 as per SOA Table 6 until DCO[d]	Eligible to continue under Protocol Amendment 04 as per SOA Table 6 until DCO[d]
Status Under Protocol Amendment 04 after DCO[d]	Not eligible to continue under Protocol Amendment 04 after DCO[d]	Not eligible to continue under Protocol Amendment 04	Eligible to continue under Protocol Amendment 04 after DCO[d] and enter PACT to receive surveillance scans[e] until stopping criteria are met[f]	Eligible to continue under Protocol Amendment 04 after DCO[d] and enter PACT to receive niraparib, SOC assessments, and surveillance scans[e] until stopping criteria are met [f g]	Eligible to continue under Protocol Amendment 04 after DCO[d] and enter PACT to receive surveillance scans[e] until stopping criteria are met[f]

a. Participants in prescreening, screening, or randomized as of the date of decision to stop enrolment (25 April 2023)
b. Screening only applies to ctDNA+ participants.
c. If ctDNA testing was started prior to the date of the decision was made to stop enrollment and the result was obtained after the date of decision to stop enrollment, and was positive, the participant will be considered part of the ctDNA+ population and currently monitored accordingly.
d. DCO is defined as the end of data collection for the planned final analyses as described in the SAP. Once the final DCO date has been reached, the clinical study database will be closed to new data.
e. Participants may continue surveillance scans per protocol, or less frequently at the discretion of the Investigator, until progressive disease/disease recurrence or participant withdraws.
f. For protocol-defined stopping criteria, please refer to Section 7.
g. SAEs, AESIs, AEs leading to discontinuation of study treatment, overdose and pregnancy reported will continue to be reported directly to the sponsor via paper form through 30 days after the last dose of study treatment. All SAEs assessed as related by the Investigator continue to be reported for all study participants until study close out and all AESIs, regardless of causality, continue to be reported for all study participants until death or loss to follow up.

Participants randomized to treatment on the ZEST study may discontinue treatment and be offered scans above standard of care, while some previously specified assessments are now discontinued. As a result of stopping enrollment, Prescreening is stopped for new patients and study assessments should be discontinued with the exception of those outlined in Table 4 and Table 5 for those participants in prescreening as of the date of the decision to stop enrollment.

Participants in Prescreening can no longer enter Screening and any participants currently in Screening as of the date of the decision to stop enrollment can no longer be randomized and should follow those outlined in Table 5.

For participants randomized in the ZEST study and on treatment as of the date of the decision to stop enrollment, the study was unblinded centrally and participants should be managed as outlined in Table 6. As of the decision to stop enrollment, PK sample collection is also discontinued along with the PK substudy.

Participants will initially enter a Prescreening Period for confirmation of detectable ctDNA (Table 2). For participants with detectable ctDNA, the Prescreening Period is followed by the Screening Period (Day -42 to Day -1) for completion of the remaining Screening assessments. It is recommended that the Screening Period start within 14 days of a confirmed ctDNA-positive result, provided all submitted prescreening tissue samples are of adequate quality per central review (Table 3). Eligible participants in Cohorts 1 and 2 are then randomized to either niraparib or placebo. For Cohort 1, a Safety Run-in as well as a PK substudy will be performed. The Safety Run-in will include the first 40 randomized participants receiving concomitant endocrine therapy. The PK substudy will include at least the first 40 randomized participants receiving endocrine therapy at sites participating in the PK substudy. Additional participants may be included in the PK substudy so that 6 participants per endocrine therapy are included, if feasible.

The Niraparib/Placebo Treatment Period is followed by an End of Treatment (EOT) Visit occurring within 7 days of last dose, a Safety Follow-up Visit 30 (+7) days after last dose, and Post-treatment Follow-up with assessments every 90 (±14) days for 2 years after the last dose and every 180 (±14) days thereafter.

Patient-reported outcomes (PROs), including the 30-question European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module (EORTC-QLQ-C30), 6-question EuroQoL 5-dimensional questionnaire 3-level version (EQ-5D-3L), single-item Patient Global Impression of Severity (PGIS)/Patient Global Impression of Change (PGIC), and Functional Assessment of Cancer Therapy-General Population (FACT-GP5), as well as a subset of approximately 15 questions from the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), will be collected approximately every 28 days (aligned with the regular participant monitoring schedule) during the Treatment Period, at the EOT Visit, at the Safety Follow-up Visit, and at the first 2 Post-treatment Follow-up assessments.

ctDNA Prescreening:

Participants must sign a ctDNA Prescreening informed consent form (ICF) consenting to collection of tumor tissue samples for ctDNA assay design and t*BRCA* and HRD testing as well as blood samples for ctDNA testing. Sufficient archival tumor tissue to establish the ctDNA platform and to perform t*BRCA* and HRd testing using the CCI [redacted] is a requirement for study entry to enable this testing. This ctDNA Prescreening, utilizing the Signatera test for ctDNA, requires an archival tissue sample from the primary tumor, including pathology reports for all tumor tissue samples, a blood sample for whole exome sequencing (WES), and subsequent ctDNA blood samples, as described in Table 2 and Table 3.

As a result of the decision to stop enrollment, prescreening procedures will be stopped, including ctDNA testing, except as outlined in Section 1.3, Table 4, and Table 5. Ongoing prescreen participants who are ctDNA-negative and <12 months from end of definitive therapy on the date of the decision to stop enrollment may continue prescreening procedures as outlined above. Upon receiving a detectable ctDNA result by the Signatera test, these participants will not receive further ctDNA tests and will proceed according to Table 4. Prescreen participants who are ctDNA+ as of the date of the decision to stop enrollment will follow Table 5. Participants who are deemed prescreen failures under previous versions of the protocol will not be reconsented and will not return for any prescreening procedures.

The Prescreening ICF can be signed either after the participant's last intervention (after surgery if adjuvant treatment is not indicated or after adjuvant treatment) and/or during chemotherapy and radiation adjuvant treatment. The timing of tumor tissue and blood sample collection in Prescreening is outlined in Table 2. It is recommended that initial testing for ctDNA is conducted as close to the end of adjuvant therapy as possible.

Participants in prescreening will have ctDNA testing performed with a maximum of 18 tests over a period of up to 6 years after end of definitive therapy for participants with a known *BRCA*mut (TNBC or HR+) and a maximum of 10 tests performed over a period of up to 2 years for participants with TNBC *BRCA*wt/unknown, as described in Table 13.

Table 13 Prescreening Consent and ctDNA Testing Frequency

	Known *BRCA*mut (TNBC or HR+)	TNBC *BRCA*wt/unknown
Time of entry since completion of end of definitive therapy (only for new patients under Protocol Amendment 02)	Anytime within 5 years	Consent within 12 weeks First ctDNA test within 16 weeks
Maximum number of ctDNA tests	Up to 18 tests over up to 6 years post-end of definitive therapy, until ctDNA-positive result or study end, whichever happens first	Up to 10 tests over up to 2 years post-end of definitive therapy, until ctDNA-positive result or study end, whichever happens first
Frequency of Testing (relative to end of definitive therapy)		
Month 0 to Month 6	Every 8 weeks ±2 weeks[a]	
Month 6 to Month 24	Every 12 weeks ±4 weeks	
Month 24 to 6 years	Every 6 months (±4 weeks)	Not applicable

a. Participants who are either under ongoing Prescreening at the time of implementation of Protocol Amendment 02, or who are re-entering prescreening should resume ctDNA testing at the time of consent to Protocol Amendment 02 and continue testing with the frequency and duration defined by the time relative to end of definitive therapy. For example, a TNBC *BRCA*wt patient re-entering prescreening at 21 months from the end of definitive therapy may test for ctDNA at 21 months and 24 months, then stop.

As of the date of the decision to stop enrollment in the ZEST study, this is no longer applicable due to changes in ctDNA testing frequency for remaining participants on study (see Section 1.3).

Under Protocol Amendment 02, participants who were deemed prescreen failures under previous versions of the protocol due to negative ctDNA test results may have the opportunity to re-enter prescreening if they meet all eligibility criteria in this protocol amendment, meet staging criteria as outlined in Prescreening criterion P2, and remain within the prescreening testing duration windows described in Prescreening criterion P4 (also see Table 14).

Participants under ongoing Prescreening at the time of implementation of Protocol Amendment 02 are eligible for additional ctDNA testing provided they continue to meet all eligibility criteria in this protocol amendment and remain within the prescreening testing duration windows described in Prescreening criterion P4. (Also see Table 14)

Table 14 Prescreening Stage, Consent, and Testing Window Requirements for Protocol Amendment 02 Participants[a]

	New Patients (enrolled in Amendment 02)	Current Patients in Ongoing Prescreening at the Time of Protocol Amendment 02 Implementation	Prior Prescreen failure Participants Re-entering the Study Under Protocol Amendment 02
Stage	Must meet Prescreening eligibility criteria for Protocol Amendment 02: Prescreening criterion P2 a,b,c	Must have Stage I-III non-metastatic primary invasive breast cancer as per Prescreening criterion P1.	Must meet Prescreening eligibility criteria for Protocol Amendment 02: Prescreening criterion P2 a,b,c
Protocol Amendment 02 Consent Window	TNBC t*BRCA*wt/unk: Must sign no later than 12 weeks from end of definitive therapy Known t*BRCA*mut (HR+ and TNBC): Must sign no later than 5 years from end of definitive therapy	Not applicable	Not applicable
ctDNA Testing Window	TNBC t*BRCA*wt/unk: Must start ctDNA testing no later than 16 weeks from end of definitive therapy Known t*BRCA*mut (HR+ and TNBC): Must start no later than 5 years from end of definitive therapy	TNBC t*BRCA*wt/unk: May continue ctDNA testing so long as no more than 24 months has elapsed since the end of definitive treatment. Known t*BRCA*mut (HR+ and TNBC): May continue ctDNA testing so long as no more than 6 years has elapsed since the end of definitive treatment.	TNBC t*BRCA*wt/unk: May resume ctDNA testing so long as no more than 24 months has elapsed since the end of definitive treatment. Known t*BRCA*mut (HR+ and TNBC): May resume ctDNA testing so long as no more than 6 years has elapsed since the end of definitive treatment.
Additional Requirements	Not applicable	To be considered "ongoing", participant must have at least 1 additional ctDNA test left per the previous testing schedule and has not yet been deemed a Prescreen fail.	Not applicable

a. Participants must also meet all other Prescreening eligibility criteria (P1 to P9; see Section 5) as per protocol in order to be eligible for ctDNA prescreening testing.

As of the date of the decision to stop enrollment, this is no longer applicable as there will be no new prescreening participants and prior prescreen failure participants are not allowed to re-enter the study.

The ctDNA testing will be reserved to participants who, from the Investigator's perspective, are at a significant risk of disease recurrence and do not present radiological or clinical signs of disease recurrence.

For participants with TNBC who are receiving adjuvant pembrolizumab following surgery, the first ctDNA test may occur during adjuvant pembrolizumab treatment provided that all adjuvant radiation and adjuvant chemotherapy have been completed (if indicated), and according to the schedule outlined in Table 2 (footnote a). Participants on adjuvant pembrolizumab who are found to have detectable ctDNA and are otherwise eligible for the study will be allowed to start niraparib concurrently with the remaining cycles of adjuvant pembrolizumab.

A participant can move to the Screening Period once detectable ctDNA is confirmed in Prescreening, provided all submitted prescreening tissue samples are of adequate quality per central review. ctDNA results will be blinded after randomization.

BRCA Tumor Mutational Status Testing:

During ctDNA Prescreening, tumor tissue samples from all participants will be collected for confirmatory central t*BRCA* testing for eligibility considerations using the CCI [redacted]

Participants with HR+/HER2− breast cancer must have a known and documented deleterious or suspected deleterious t*BRCA*mut (either *sBRCA* or *gBRCA* positive) and meet all other prescreening eligibility criteria to qualify for ctDNA Prescreening and must have been on a stable regimen of endocrine therapy for a minimum of 3 months prior to randomization. Participants with HR+/HER2− breast cancer who have t*BRCA*mut confirmed by central testing will be eligible for Cohort 1; if central testing does not confirm a t*BRCA*mut in HR+/HER2− participants, they will not be eligible for the study. Participants with TNBC who have centrally confirmed t*BRCA*mut will be eligible for enrollment in Cohort 1, and those who are t*BRCA*wt or who have undetermined t*BRCA* status will be eligible for enrollment in Cohort 2. Note that the confirmatory central t*BRCA* test does not distinguish between somatic and germline *BRCA* mutations and does not replace standard germline testing.

As a result of the decision to permanently stop enrollment, no further *tBRCA* testing using CCI [redacted] will be conducted for any participants, regardless of ctDNA status. All participants randomized prior to the date of the decision to stop enrollment have had confirmatory central *tBRCA* testing completed by the CCI [redacted] assay under previous versions of the protocol.

Tumor HRD Status Testing

Tumor tissue samples collected at Prescreening will be used for centralized testing using CCI [redacted] to classify participants in Cohort 2 by HRD status.

As a result of the decision to permanently stop enrollment, no further HRD status assessment using the CCI [redacted] will be conducted for any patient, regardless of ctDNA status. All participants randomized prior to the date of the decision to stop enrollment have had HRD assessment testing by CCI [redacted] assay completed under previous versions of the protocol.

Screening Period:

As a result of the decision to permanently stop enrollment, participants can no longer enter Screening. Participants currently in Screening as of the date of the decision to stop enrollment that decide to remain on study will follow Table 5.

During the Screening Period, participants will sign the main study ICF and complete all remaining assessments required to determine eligibility for the study. The Screening Period is within 6 weeks (42 days) of Cycle 1/Day 1 and is recommended to start within 14 days of a confirmed ctDNA-positive result, provided all submitted prescreening tissue samples are of adequate quality per central review. All screening criteria (unless

otherwise specified in Table 3) are required to be repeated if they fall outside of 6 weeks prior to first dose.

All participants are required to have documented presence of ctDNA, central confirmation of t*BRCA*mut status, and no evidence of overt recurrent/metastatic disease prior to being randomized 1:1 to either niraparib or placebo.

Randomization and Stratification:

As of the date of the decision to stop enrollment, participants can no longer be randomized.

Participants in Cohort 1 will be stratified based on the following factors:

- Time from last intervention (defined in Section 6.3.2) to randomization (<6 months versus ≥6 months)
- HR status (positive versus negative)
- Prognostic Stage of breast cancer (Stage I/II versus Stage III) (Appendix 13)

Participants in Cohort 2 will be stratified based on the following factors:

- Time from last intervention (defined in Section 6.3.2) to randomization (<6 months versus ≥6 months)
- Prior use of adjuvant capecitabine (yes versus no)
- Prognostic Stage of breast cancer (Stage I/II versus Stage III) (Appendix 13)

Safety Run-in Period (Cohort 1):

As of the date of the decision to stop enrollment, Safety Run-in is no longer applicable. A total of 40 participants were randomized in the study.

A Safety Run-in Period will be conducted in the first 40 randomized participants in Cohort 1 who are taking endocrine therapy (anastrozole, letrozole, exemestane, and tamoxifen, with or without ovarian function suppressing agents). All participants receiving concomitant endocrine therapy need to have been on a stable regimen of endocrine therapy for a minimum of 3 months prior to randomization. While on study, the endocrine regimen can be interrupted or discontinued as clinically indicated. During the Treatment Period, the endocrine regimen may be exchanged for another regimen after discussion with the GSK Medical Monitor, but the regimen may not be changed during the Safety Run-in Period or the PK substudy.

CCI

[redacted]

As of the date of the decision to stop enrollment, assessment by an IDMC is no longer needed due to enrollment being permanently stopped and the study being centrally unblinded.

Study Conduct:

As of the date of the decision to stop enrollment, several study procedures described below are no longer applicable. **As of Protocol Amendment 04, participants should be managed as outlined in Table 12 and Section 1.3. Once PACT Phase is implemented, participants will be managed as per Section 6.7.1.**

Participants who meet all eligibility criteria will be randomized in a 1:1 ratio to receive niraparib or placebo.

Clinic visits will occur on Day 1 of each cycle (Table 3). Hematology laboratory values will be monitored weekly for the first 28-day cycle of the Niraparib/Placebo Treatment Period, and blood pressure (BP) and heart rate (pulse) will be monitored weekly for the first two 28-day cycles of the Niraparib/Placebo Treatment Period. If participants are unable to attend clinic visits on Cycle 1/Day 1 (postdose), Cycle 1/Day 15, and Cycle 2/Day 1 (postdose), they must have assessments for these visits performed through at-home nursing on the date the visit would have occurred. If participants are unable to attend clinic visits on Cycle 1/Day 8, Cycle 1/Day 22, Cycle 2/Day 8, Cycle 2/Day 15, and Cycle 2/Day 22, they must have the assessments for these visits performed either through a local laboratory/clinic or through at-home nursing on the date the visit would have occurred. At-home nursing services are to be used as per investigator discretion for COVID-related accommodations where needed, and/or to reduce frequent visit burden for participants. Further details are outlined in Section 8.1.1. As of the date of the decision to stop enrollment, at-home nursing services will no longer be offered.

All participants are required to undergo tumor imaging as provided below and all imaging data acquired with the purpose of tumor assessment must be submitted to the Imaging Vendor for Central Review. As of the date of the decision to stop enrollment, imaging does not need to be submitted to the imaging vendor for central review. Imaging will be conducted for ongoing participants as outlined in Section 1.3, Table 4, Table 5, and Table 6. The preferred imaging method is IV contrast-enhanced CT, and a bone scan. The same imaging method and anatomical coverage should be used throughout the study.

- Baseline:
  - An IV contrast-enhanced CT scan of the chest/abdomen/pelvis and a bone scan will be conducted within 42 days (6 weeks) prior to randomization (as outlined in Table 3).
  - If IV CT contrast cannot be used (e.g., sensitivity to CT contrast or contrast shortage): Noncontrast CT of the chest and IV contrast-enhanced magnetic resonance imaging (MRI) of abdomen/pelvis, and a bone scan.

    If both IV CT and IV MRI contrast cannot be used, or if renal insufficiency: noncontrast CT of chest/abdomen/pelvis, and a bone scan. If MRI is performed at Baseline, it should be preferentially continued throughout the study. If brain metastasis is suspected, IV contrast-enhanced MRI is preferred over IV contrast-enhanced CT for imaging of the brain.

- On study: An IV contrast-enhanced CT scan of the chest, abdomen, and pelvis (or IV contrast-enhanced MRI of abdomen and pelvis and noncontrast CT of chest, if MRI performed at Baseline) will be conducted every 12 weeks (84±7 days) from date of randomization for the first 2 years and every 24 weeks (168±7 days) thereafter, or more frequently as clinically indicated (unscheduled), until Investigator assessment of disease recurrence using RECIST v1.1. Bone scans should only be performed postbaseline if clinically indicated. If brain metastasis is suspected, IV contrast-enhanced MRI is preferred over IV contrast-enhanced CT for imaging of the brain.

If a participant discontinues study treatment for any reason other than disease recurrence, death, withdrawal of consent, or loss to follow-up, then scans should continue at the specified intervals until recurrence is confirmed.

Each participant will have an EOT Visit at the time of discontinuation from study treatment, a Safety Follow-up Visit 30 (+7) days after last dose, and Post-treatment Follow-up with assessments every 90 (±14) days for 2 years after the last dose and every 180 (±14) days thereafter, which will continue until death or the end of study data collection (provided that this allows the opportunity for completion of all follow-up assessments). Information regarding subsequent anticancer treatments (including regimen and number of cycles), as well as the date of any subsequent PD (ie, for determination of progression on next anticancer therapy), hospitalization, and other supportive care and procedures (eg, surgery or radiation), and survival status will be collected during these assessments.

GSK may request that updated survival data be collected on all treated/randomized participants outside the protocol window noted in the Schedule of Activities (SOA) (Table 3). At the time of the request, the site will determine survival status for each participant by the method agreed with the participant, unless the participant has withdrawn consent from the study.

Reporting of safety events will begin at the time of ctDNA Prescreening ICF signature date only for events related to ctDNA and WES blood sample collection procedures. All AEs and serious adverse events (SAEs) will be collected and recorded for each participant from the day of signing the main study ICF until 30 days after last dose of study treatment or start of new anticancer therapy. All AEs and SAEs experienced by a participant, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the participant is lost to follow-up, or until the participant has died. All SAEs assessed by the Investigator as related to the study treatment and all adverse events of special interest (AESIs), regardless of causality, will be collected and reported until study closeout, or as otherwise indicated. Any pregnancies that occur within 180 days post-treatment will be reported.

Participants will continue to receive their assigned treatment until disease recurrence as assessed by RECIST v1.1, death, withdrawal of consent, loss to follow-up or until unacceptable toxicity. Those participants who have completed 39 cycles (approximately 3 years) with no evidence of recurrence will have the option to either continue treatment or stop treatment at that time. If available, participants continuing niraparib treatment at the time of final analysis may be offered the option to continue to receive niraparib

treatment. Dose interruptions, reductions, or treatment discontinuation may be implemented at any time according to the dose modification guidelines in this protocol (Section 6.4) and under the discretion of the Investigator.

For all participants in Cohort 1 and Cohort 2, blood samples will be collected in the main study at Cycle 1/Day 1, Cycle 1/Day 15, Cycle 2/Day 1, Cycle 4/Day 1, and Cycle 8/Day 1, as specified in Table 7 for sparse PK sampling to characterize niraparib exposure in participants with breast cancer and to explore the relationship between exposure to niraparib and responses in efficacy and safety.

A subset of participants in Cohort 1 will have additional blood samples collected in a PK substudy. The PK substudy will include at least the first 40 randomized participants receiving endocrine therapy at sites participating in the PK substudy. The samples collected in the PK substudy will be analyzed to characterize the steady-state PK of endocrine therapy and to assess any potential effect of niraparib on endocrine therapy exposure, as data permit. Based on the randomized nature of the study, it is assumed that approximately 20 participants in the PK substudy will be receiving endocrine therapy with niraparib, while the remaining participants will be receiving endocrine therapy with placebo, allowing for a comparison of endocrine therapy PK with or without niraparib co-administration. Additional participants may be included in the PK substudy if there are too few participants receiving any of the individual endocrine therapies to meet the objectives of the substudy; if feasible, 6 participants per endocrine therapy will be targeted. The samples for the PK substudy will be collected at Cycle 1/Day 15 as specified in Table 8, at which time niraparib exposure will have reached steady state.

4.2. Scientific Rationale for Study Design

Despite recent advances made in the treatment of TNBC and HR+/HER2− breast cancer, an urgent unmet medical need exists for effective therapeutic options to delay metastatic breast disease following definitive therapy. This study will include the following cohorts:

- Cohort 1: participants with HER2− breast cancer (independent of HR status) who have tumors that are t*BRCA*mut and have detectable ctDNA
- Cohort 2: participants with TNBC who have tumors that are t*BRCA*wt and have detectable ctDNA

For Cohort 1, the decision to enroll all participants with t*BRCA*mut HER2− breast cancer to a single cohort, despite differences in HR status, is based on the observed efficacy of niraparib in *BRCA*mut ovarian tumors, preliminary clinical activity of niraparib as neoadjuvant in t*BRCA*mut HER2− breast cancer, and the observed efficacy of other PARP inhibitors in metastatic g*BRCA*mut breast tumors independent of HR status. Efficacy analyses will be stratified by HR status to determine the effect of niraparib on each participant population.

Cohort 2 will enroll participants with t*BRCA*wt TNBC who have detectable ctDNA following completion of definitive therapy. The unmet medical need for antitumor therapy in participants with TNBC is independent of t*BRCA* status. The results from the NOVA and PRIMA studies of niraparib indicate a consistent continuum of clinical benefit across biomarker-defined subpopulations and that the benefit of niraparib treatment extends beyond participants with *BRCA*mut disease (Section 2.2.5.1). This

observation is not limited to niraparib or ovarian cancer. In Study 3000-PN162-01-001 (TOPACIO/KEYNOTE-162), combination treatment with niraparib and pembrolizumab demonstrated clinical activity in participants with TNBC, irrespective of *BRCA* mutation status, with the greatest activity observed in participants with t*BRCA*mut tumors (Section 2.2.5.2). Studies demonstrating the activity of other PARP inhibitors in TNBC are summarized in Section 2.1.

The following aspects of the study design are discussed in more detail below:

- The choice of placebo as the comparator arm
- Justification for t*BRCA*/HRD assay
- The ctDNA method
- Justification of enrichment of Stage II to III and non-pCR patients
- Justification of ctDNA testing frequency and timing

Justification of Comparator Arm

Placebo was chosen as the comparator arm as there is currently no available standard-of-care therapy for patients who have detectable ctDNA following their last intervention (surgery or adjuvant therapy). Ongoing long-term hormonal therapies as backbone therapy in HR+ participants are allowed (eg, aromatase inhibitors, tamoxifen) in Cohort 1.

A conceptually similar approach has led to regulatory approval of drugs delaying the onset of radiologically detectable metastasis in biochemically recurrent (=low disease burden) non-metastatic castration-resistant prostate cancer where placebo was also used as the comparator arm and participants continued to receive backbone hormonal ablation therapy in both treatment arms [Fizazi, 2019; Smith, 2018].

While results from the OlympiA trial noted in Section 2.2.4 demonstrated improved IDFS with adjuvant olaparib treatment in patients with high-risk Stage II to III *gBRCA*mut HER2− breast cancer, those eligible for Cohort 1 in this study are a subset of patients with *BRCA*mut that are not eligible for treatment with olaparib due to one or more of the following criteria:

- TNBC patients who received adjuvant therapy and who have T1 and/or node-negative disease;
- Those patients who already completed definitive therapy in the past and fall outside the traditional adjuvant 12-week window defined by OlympiA; and
- Those with a s*BRCA*mut, and
- Those who do not otherwise meet criteria for adjuvant olaparib treatment per local guidelines

In these settings, enrollment into this ZEST study remains an appropriate option for patients and, given the absence of any standard of care alternatives, the use of placebo in the comparator arm is medically justified.

Justification for t*BRCA*/HRD Assay

CCI [redacted]. This assay has been analytically validated in breast cancer and is CE marked, which supports its use in investigational studies of PARP inhibitors.

Justification of ctDNA Method

The Signatera test, the method chosen for use in this study, requires an archival tissue sample of the primary tumor, including pathology reports for all tumor tissue samples, and blood samples from each participant. The tumor tissue sample and a blood sample are used for WES to identify tumor-specific somatic variants by comparing the WES profile of the primary tumor (somatic DNA) with that of matched white blood cells (germline DNA). To determine whether observed somatic variants are found in all tumor cells or a subset of tumor cells, clonality inference is performed as described by McGranahan et al [McGranahan, 2015]. CCI [redacted]

CCI [redacted]

CCI [redacted] The risk of recurrence for patients with TNBC is

highest during the first 2 to 3 years following the completion of standard therapy for curative intent [Cortazar, 2014]. The main period of screening for ctDNA covers a 24-month period following the end of therapy for curative intent. The ctDNA test is expected to identify molecular detectable disease on average approximately 9 months ahead of clinical or radiologic progression; therefore, 24 months should allow for identification of a large proportion of participants with risk of recurrence. A more distant time point from the end of the curative intent therapy is also included to capture some participants who would progress later, particularly participants with HR+ disease, who are known to have a slower rate of recurrence over time. In cases where surgery is the last step of curative intent therapy, a minimum 4-week interval is proposed to allow elevated circulating free DNA that is released from surgical trauma to normalize [Henriksen, 2020]. For participants receiving pembrolizumab, the schedule of ctDNA assessment is outlined in Table 2 (footnote a) based on data from Bratman et al [Bratman, 2020] to allow for adequate opportunity for ctDNA nadir to occur with adjuvant pembrolizumab.

Justification for Enrichment of Stage II to III and non-pCR Patients

The eligible population for ZEST prescreening has been amended in the current protocol amendment to enrich for participants most likely to develop detectable ctDNA, which are those participants with higher stage disease at the time of diagnosis and those participants who did not achieve a pCR following neoadjuvant therapy. Several recent studies have shown that the detection rate of ctDNA in breast cancer patients differs significantly across tumor stages [Riva, 2017; Cavallone, 2020; Molinero, 2022; Yoshinami, 2020]. In a study of 46 patients with TNBC, the ctDNA detection rate at diagnosis was 0%, 77%, and 100% in patients with Stage I, II, and III disease, respectively [Riva, 2017]. Another study reported 0.01% in Stage I, 1.15% in Stage II, and 9.73% in Stage III [Cavallone, 2020].

Another clinicopathological feature related to ctDNA incidence is presence or lack of residual disease after neoadjuvant therapy. In a cohort of 84 high-risk early breast cancer patients in the neoadjuvant chemotherapy I-SPY 2 trial using the Signatera ctDNA assay, authors demonstrated that after NAC, all patients who achieved pCR were ctDNA-negative (n=17, 100%). For those who did not achieve pCR (n=43), ctDNA-positive patients (14%) had a significantly increased risk of metastatic recurrence (hazard ratio=10.4; 95% CI: 2.3 to 46.6). Patients who did not achieve pCR but were ctDNA-negative (86%) had an excellent outcome, similar to those who achieved pCR (hazard ratio=1.4; 95% CI: 0.15 to 13.5) [Magbanua, 2021].

In short, the literature to date suggests that ctDNA detectability appears to mirror classic “high-risk” features for breast cancer recurrence, such as higher stage at diagnosis and non-pCR following neoadjuvant therapy. These findings support the decision to modify the prescreening population for future prescreening participants in the ZEST trial.

Justification of ctDNA Testing Frequency and Timing in Prescreening

Under Protocol Amendment 02, the timepoints for starting ctDNA testing and the frequency of testing are outlined in Table 13 and Figure 3. For new study participants with HR+/HER2- *BRCA*mut breast cancer and TNBC *BRCA*mut (*BRCA*mut [TNBC or HR+]; Cohort 1), ctDNA surveillance can start up to 5 years from the end of definitive therapy, while new participants with TNBC that do not carry *BRCA* mutation or where

local *BRCA* test was not performed (TNBC *BRCA*wt/unknown; Cohort 2) are required to sign the prescreening informed consent within 12 weeks from the end of definitive therapy. The reason for restricting the time from the end of definitive therapy for TNBC *BRCA*wt/unknown (Cohort 2) is to identify fast molecular progressors early on, post completion of curative-intent treatment, and before radiological relapse is detected. However, a wider window of enrollment is allowed for Cohort 1 (*BRCA*mut [TNBC or HR+]); for several reasons. Most importantly, patients with a *BRCA* mutation that fall beyond 12 weeks of completion of definitive therapy, as based on the OlympiA study, would not be eligible for Lynparza (olaparib) treatment, and are a population with an unmet medical need [Tutt, 2021]. To that end, the ZEST study design offers ctDNA testing to patients with a *BRCA* mutation that have been identified past the time of eligibility for the OlympiA trial, and therefore, are not eligible for olaparib treatment beyond this 12-week window. Enrollment is allowed for up to 5 years since end of definitive therapy to allow ample time for identification of *BRCA*mut patients who may have previously been treated but are more recently found to carry a mutation as standard-of-care genetic testing practices evolve. Further, it has recently been shown that development of ctDNA detectability among HR+/HER2– patients may be delayed for several years after diagnosis [Lipsyc-Sharf, 2022], which also supports the prolonged recruitment window. The number of tests a participant is being offered in the ZEST trial is a maximum of 10 tests for patients with TNBC and t*BRCAwt*/unknown or up to 18 tests for TNBC or HR+ breast cancer patients with t*BRCAmut* but for up to 6 years since end of definitive therapy, ctDNA-positive result, or end of study, whichever occurs first. The frequency of tests is outlined in Figure 3.

The revised testing schedule in Protocol Amendment 02 applies to participants newly referred for prescreening and to ongoing participants in prescreening, but also may be offered to previously prescreened participants that tested negative for ctDNA and who meet Prescreening criteria P2 and P4, and all the other prescreening eligibility criteria. The rationale for additional testing is derived from the literature data suggesting ctDNA prevalence in patients tested more than 18 months since definitive therapy is 3% in TNBC and ranges between 4% and 25% in HR+/HER2– breast cancer [Olsson, 2015; Garcia-Murillas, 2019; Coombes, 2019; Turner, 2021].

In line with maximizing early detection of ctDNA+ patients, prior to radiological relapse in participants receiving pembrolizumab treatment, ctDNA testing is recommended to start within 12 weeks from first pembrolizumab dose in any setting. Data from Magbanua et al. [Magbanua, 2021], summarized above, provide confidence that ctDNA status post neoadjuvant chemotherapy is a good predictor of outcome. To that end, additional 12 weeks of treatment with pembrolizumab in the adjuvant setting is not required prior to testing for ctDNA.

4.3. Justification for Dose

The starting dose of niraparib is based upon the participant's hepatic function and baseline body weight and/or baseline platelet count. Normal or mildly impaired hepatic function is defined as either AST >ULN and total bilirubin ≤ULN; or any AST and total bilirubin >1.0× to 1.5× upper limit of normal (ULN). Moderately impaired hepatic function is defined as total bilirubin >1.5× and ≤3×ULN and any level of AST elevation.

In participants with normal or mildly impaired hepatic function, the niraparib starting dose is 300 mg orally once daily in participants with a baseline body weight ≥77 kg and baseline platelet count ≥150,000/µL and 200 mg orally once daily in participants with a baseline body weight <77 kg or baseline platelet count <150,000/µL. The dose is based on observations from previous niraparib studies that identified body weight and platelet count as clinical factors associated with Grade 3/4 thrombocytopenia events. These observations were confirmed in the PRIMA study, in which an individualized starting dose (200 mg in participants <77 kg or with a baseline platelet count <150,000/µL; 300 mg in participants with ≥77 kg and a platelet count ≥150,000/µL) allowed participants to achieve comparable efficacy with a substantially lower incidence of thrombocytopenia and anemia.

In participants with moderate hepatic impairment, the niraparib starting dose is 200 mg orally once daily in all participants, regardless of baseline body weight or baseline platelet count. This recommendation is based on results of a study of niraparib in participants with normal hepatic function and moderate hepatic impairment (Study 3000-01-003). Due to the expected effect of hepatic impairment on niraparib disposition, the starting dose is reduced from 300 mg to 200 mg once daily for participants with moderate hepatic impairment, weight ≥77 kg, and platelet count ≥150,000/µL in order to minimize the risk of thrombocytopenia while still maintaining niraparib exposures in a range associated with efficacy in the PRIMA study.

4.4. End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the study. As a result of the decision to permanently stop enrollment, the study will conclude when the last participant has completed their last study procedure (as outlined in Section 1.3).

Participants will remain on study until discontinuation/withdrawal from the study or the end of study data collection. (Reasons for participant discontinuation/withdrawal are provided in Section 7.2.) If a participant dies, the cause of death should be documented in the electronic case report form (eCRF). 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, is no longer being followed at the Investigator's discretion, or if the study is closed/terminated.

The end of study (EOS) is defined as the date of the last visit of the last participant in the study or last scheduled procedure for the last participant in the study. Note: Participants are considered ctDNA+ if the result of ctDNA testing was positive as of the date of the decision to stop enrollment in the ZEST study. If ctDNA testing was started prior to the date of the decision was made to stop enrollment and the result is obtained after the date of the decision to stop enrollment, and was positive, the participant will be considered part of the ctDNA+ population and currently monitored accordingly. For any additional ctDNA samples taken/tested after the date of the decision to stop enrollment, the testing process outlined in Table 12 should be followed. For participant management under Protocol Amendment 04, refer to Table 12. Once the last participant consents to Protocol Amendment 04 (or withdraws) or meets any protocol-defined stopping criteria (Section 7), the study will transition to PACT.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Enrollment of new participants is permanently stopped due to Sponsor decision.

Prescreening

To qualify for Prescreening, participants must meet the following criteria:

P1. Histologically confirmed Stage I to III non-metastatic primary invasive breast cancer that is one of the 2 following phenotypes:

a. TNBC defined as:

- ER and PgR negative, defined as IHC nuclear staining <1%, and
- HER2– defined as follows:
  - IHC 0, 1+ without ISH, or
  - IHC 2+ and ISH non-amplified as defined by 2018 ASCO-CAP guidelines [Wolff, 2018]

b. ER and/or PgR positive, HER2– breast cancer defined as follows:

- ER and/or PgR positive, defined as IHC nuclear staining ≥1%, and
- HER2– defined as follows:
  - ICH 0, 1+ without ISH, or
  - IHC 2+ and ISH non-amplified as defined by 2018 ASCO-CAP guidelines [Wolff, 2018]

Participants with multifocal tumors are eligible provided that all lesions are within the same quadrant and have similar ER, PgR, and HER2 staining. Multicentric and synchronous bilateral breast cancers are not allowed.

For participants who received neoadjuvant therapy and have discordant ER, PgR, and/or HER2 receptor results between the diagnostic biopsy (pretreatment) and surgical pathology (post neoadjuvant therapy), the receptor status of the pretreatment specimen determines eligibility. If the biopsy and the surgical specimens are discrepant in the adjuvant setting (i.e., participants had initial surgery), results from the surgical specimen define HR status. Those participants determined to be TNBC based on the pretreatment specimen should not subsequently receive tamoxifen or aromatase inhibitor as part of their breast cancer treatment.

Note: ER and PgR may be graded using the Allred scoring system, where TNBC is defined to be 0 out of 8 or 2 out of 8, or staining in <1% of cancer cells and HR+ is defined to be a score of ≥3 out of 8.

P2. New participants joining the study (i.e., have not previously provided Prescreening consent prior to Protocol Amendment 02) must meet the following criteria:

a. **For participants who underwent initial surgery (Adjuvant approach)**:

- TNBC participants must meet at least 1 of the following criteria:
  - Node-positive (≥pN1, any tumor size), or
  - Node-negative (pN0) or axillary node micro-metastasis (pN1mi) with invasive primary tumor ≥15 mm
- HR+ participants must meet at least 1 of the following criteria:
  - Node-positive with ≥4 involved nodes (≥pN2, any tumor size), or
  - Node-negative (pN0) or axillary node micro-metastasis (pN1mi) with invasive primary tumor >5 cm (≥pT3), or
  - Either node-positive with 1 to 3 involved nodes (pN1) OR node-negative or axillary node micro-metastasis with invasive primary tumor >2 cm but ≤5 cm (pT2N0 or pT2N1mic). Invasive tumor must also meet 1 of the following:
    - Grade 3
    - Grade 1 or 2 with ER+/PgR-
    - Grade 1 or 2 with ER-/PgR+

b. For patients who underwent neoadjuvant chemotherapy followed by surgery (Neoadjuvant approach):

- All participants must have shown a definitive response to preoperative chemotherapy by pathological, radiological, or clinical evaluation (see Appendix 1)
- TNBC participants must have residual invasive breast cancer in the breast and/or resected lymph nodes (non-pCR) (any grade is allowed)
- HR+ participants must have residual invasive breast cancer in the breast and/or resected lymph nodes (non-pCR), AND meet 1 of the following criteria:
  - Node-positive prior to or after neoadjuvant treatment (≥cN1 or ≥pN1, any tumor size),
  - Invasive primary tumor size >2 cm prior to or after neoadjuvant treatment (≥cT2 or ≥pT2),

c. For HR+ participants who underwent neoadjuvant endocrine-only therapy, followed by surgery (Neoadjuvant approach, but without any preoperative chemotherapy)

- All participants must have shown a definitive response to preoperative endocrine therapy by pathological, radiological, or clinical evaluation (see Appendix 1)
- HR+ participants must have residual invasive breast cancer in the breast and/or resected lymph nodes (non-pCR), AND meet 1 of the following criteria:
  - Node-positive with ≥4 involved nodes (≥pN2, any tumor size), or
  - Node-negative (pN0) or axillary node micro-metastasis (pN1mi) with invasive primary tumor >5 cm (≥pT3), or
  - Either node-positive with 1 to 3 involved nodes (pN1) OR node-negative or axillary node micro-metastasis with invasive primary tumor >2 cm but ≤5 cm (pT2N0 or pT2N1mic). Invasive tumor must also meet 1 of the following:
    - Grade 3
    - Grade 1 or 2 with ER+/PgR-
    - Grade 1 or 2 with ER-/PgR+

Participants who previously completed Prescreening under previous versions of the protocol and who are deemed to have been Prescreen failures due to negative ctDNA testing results on all allotted tests may re-enter Prescreening provided they are eligible to continue Prescreening testing as per protocol (see criterion P4) AND meet all staging criteria as defined above in criterion P2 a to c.

Participants who are currently participating in ongoing Prescreening at the time of Protocol Amendment 02 consent, and who are eligible to continue Prescreening testing as per protocol (see criterion P4), must have Stage I to III non-metastatic primary invasive breast cancer as per criterion P1, but are not required to meet staging criteria as defined in criterion P2 a to c. As of the date of the decision to stop enrollment, prior prescreen-fail patients (who had not already signed Protocol Amendment 02 consent), are not allowed to be re-enrolled or reconsented and no further assessments or ctDNA testing are allowed.

P3. HR+ breast cancer participants must have documented mutation in *BRCA1* or *BRCA2* that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) identified through local testing.

P4. Signed prescreening consent.
New participants joining the study (i.e., that have not previously provided Prescreening consent prior to Amendment 02) must sign consent within the following timepoints:

a. **For TNBC participants (t*BRCAwt* or t*BRCA* unknown):** TNBC participants who have not been tested for t*BRCA* or have no mutation identified (t*BRCA*wt) must sign prescreening consent no later than within 12 weeks from the end of definitive therapy

- Note: Participants receiving pembrolizumab must also consent to Prescreening within 12 weeks of completing definitive therapy (i.e., curative-intent surgery, chemotherapy, and/or radiation, whichever happens last). Pembrolizumab is NOT included in the definition of definitive therapy in this protocol, and participants may continue to receive pembrolizumab as per standard of care during the study, with ctDNA testing performed according to the schedule outlined in Table 2 (footnote a)

b. **For known t*BRCA*mut TNBC or HR+ breast cancer participants:** Participants who have a known and documented deleterious **or** suspected deleterious t*BRCA* mutation identified through local testing must sign prescreening consent no later than 5 years from end of definitive therapy

Participants who are currently participating in ongoing Prescreening at the time of implementation of Protocol Amendment 02, or who completed Prescreening in the past under previous versions of the protocol, must provide Prescreening consent for additional ctDNA testing as per Protocol Amendment 02, but are not required to meet the consent timepoint windows as described in criterion P4 a to b.

Participants who are eligible to either re-enter Prescreening or to continue ongoing Prescreening ctDNA testing are those who continue to meet other prescreening eligibility criteria and meet 1 of the following criteria at the time of consent for Protocol Amendment 02:

- Participant is currently participating in ongoing Prescreening at the time of Protocol Amendment 02 implementation, has at least 1 additional ctDNA test left per the original testing schedule, and has not been deemed a Prescreen failure.
- Participant previously completed Prescreening under previous versions of the protocol and was deemed to have Prescreen-failed due to negative ctDNA testing results on all allotted tests, AND still remains within the defined testing duration window from end of definitive treatment at the time of reconsent:
  - Participants with TNBC (t*BRCA*wt or t*BRCA* unknown) may resume ctDNA testing so long as no more than 24 months has elapsed since the end of definitive treatment.
  - Participants with known t*BRCA*mut (either TNBC or HR+) may resume ctDNA testing so long as no more than 6 years has elapsed since the end of definitive treatment.

Additional ctDNA testing for participants eligible to resume or continue Prescreening testing will occur according to the schedule outlined in Table 13, Table 14, and Figure 3. As of the date of the decision to stop enrollment, prior prescreen-fail patients (who had not already signed Protocol Amendment 02 consent), are not allowed to be re-enrolled or reconsented and no further assessments or ctDNA testing are allowed.

P5. Completed prior standard therapy for curative intent, including all of the following, if indicated: neoadjuvant treatment, surgery, adjuvant radiotherapy, and adjuvant chemotherapy. Participants with HR+HER2− t*BRCA*mut breast cancer may be receiving concurrent adjuvant endocrine therapy. Participants with TNBC may receive concurrent adjuvant pembrolizumab, if clinically indicated. All participants may receive bisphosphonates or denosumab. Participants are allowed and encouraged to enter Prescreening as soon as possible per protocol, and may be eligible to start the Prescreening process prior to the completion of adjuvant therapy (see Figure 1 , Table 2, and Section 6.8 for further details of permitted concomitant medications).

P6. An archival tumor tissue specimen of the primary tumor sufficient in quality and quantity for ctDNA assay design and t*BRCA* and HRD testing is required. As of the date of the decision to stop enrollment, no further t*BRCA* and HRD testing will be performed (see Section 1.3).

NOTE: If the participant has a prior history or additional primary breast cancers, which appear eligible for prescreening in this ZEST trial (see exclusion criterion 12), the lesion considered at highest risk for recurrence based on the investigator's discretion will be used for ctDNA assay design.

P7. Have a significant risk of disease recurrence as assessed by the Investigator.

P8. Have no known or suspected locally recurrent or metastatic disease as assessed by the Investigator.

P9. Have no known nonmodifiable conflicts with other inclusion and exclusion criteria listed in Section 5.1 and Section 5.2, respectively.

To be eligible for randomization in the study, participants must meet the full inclusion and exclusion criteria presented in Section 5.1 and Section 5.2, respectively.

5.1. Inclusion Criteria

Participants must meet all prescreening criteria to be included in the study. Participants are eligible to be included in Cohorts 1 and 2 of the study only if all of the following criteria are met:

1. Stage I to III breast cancer per AJCC for breast cancer staging criteria 8th edition (see Section 8.2.1) with surgical resection of the primary tumor that is confirmed to be either:

   - TNBC, or
   - HR+/HER2− breast cancer with a known and documented deleterious or suspected deleterious t*BRCA* mutation

   Note: TNBC is defined as outlined in P1. ER and PgR may be graded using the Allred scoring system, where TNBC is defined to be 0 out of 8 or 2 out of 8, or staining in <1% of cancer cells and HR+ is defined to be a score of ≥3 out of 8.

2. Completed prior standard therapy for curative intent, including all of the following, if indicated: neoadjuvant treatment, surgery, adjuvant radiotherapy, and adjuvant chemotherapy. Participants with HR+HER2− t*BRCA*mut breast cancer may be

receiving concurrent adjuvant endocrine therapy. Participants with TNBC may receive concurrent adjuvant pembrolizumab, if clinically indicated. All participants may receive concurrent bisphosphonates or denosumab (see Figure 1, Table 2, and Section 6.8 for further details of permitted concomitant medications).

3. Participants with HR+ breast cancer must be on a stable regimen of endocrine therapy, if indicated, for at least 3 months prior to randomization. Ovarian suppression, if indicated, must also have been started at least 3 months prior to randomization.
4. Detectable ctDNA as measured by central Signatera testing (refer to Table 2 for the timing of ctDNA testing). As of the date of the decision to stop enrollment, sample collection was stopped as outlined in Section 1.3.
5. An archival tumor tissue specimen of the primary tumor sufficient in quality and quantity for ctDNA assay design and t*BRCA* and HRD testing is required. (Archival tissue must have been sent during Prescreening.) (See Prescreening criterion P6 for additional details.)
6. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Must be ≥18 years of age.
8. Must have adequate organ and bone marrow function, as defined below.

Absolute neutrophil count:	≥1,500/µL
Platelets:	≥100,000/µL
Hemoglobin:	≥9 g/dL or 5.6 mmol/L
Renal function:	Calculated creatinine clearance ≥30 mL/min
Total bilirubin:	≤3 × ULN
ALT	≤2.5 × ULN

Note: complete blood count (CBC) should be obtained without transfusion or receipt of colony-stimulating factors within 4 weeks prior to obtaining the sample. Creatinine clearance should be determined as per the Cockcroft-Gault formula.

Participants with current active liver or biliary disease are excluded (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per Investigator assessment). Participants with mild hepatic impairment are allowed, defined as either AST >ULN and total bilirubin ≤ULN;-any AST and total bilirubin >1.0× to 1.5× ULN. Participants with moderate hepatic impairment are allowed, defined as total bilirubin >1.5× to ≤3× ULN and any level of AST elevation. All participants must also have ALT ≤2.5xULN in order to be eligible for the study.

9. Participants with toxicity from prior cancer therapy must have recovered to Grade 1. (A participant with Grade 2 neuropathy or any grade of alopecia is an exception to this criterion and may qualify for this study.)
10. Must be able to swallow and retain orally administered study treatment.
11. A female participant is eligible if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

    - Is not a woman of childbearing potential (WOCBP), as defined in Appendix 4.

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described in Appendix 4 (for France, see Section 10.14.1.2 and for Germany see Section 10.14.2.3), during the Treatment Period and for at least 180 days (except in France, see Section 10.14.1.1) after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
- A WOCBP must have a negative pregnancy test (highly sensitive urine test or serum test as required by local regulations) within 72 hours before the first dose of study treatment.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study treatment are described in Section 8.4.6.
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

See Appendix 4 for a list of acceptable birth control methods (for France see Section 10.14.1.2 and for Germany see Section 10.14.2.3). Information must be captured appropriately within the site's source documents.

12. Male participants are eligible if they agree to the following during the Treatment Period and for at least 90 days (except France, see Section 10.14.1.1) after the last dose of study treatment (see Appendix 4 for a list of acceptable birth control methods; for France see Section 10.14.1.2 and for Germany see Section 10.14.2.3):

    - Be abstinent from intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

    OR

    - Must agree to use contraception/barrier as detailed below:
        - Agree to use a male condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak)

    PLUS

        - Male participants must refrain from donating sperm for at least 90 days after the last dose of study treatment (except in France, see Section 10.14.1.1)

13. Must be able to understand the study procedures and agree to participate in the study by providing written informed consent (as described in Appendix 5), which includes

compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from Cohorts 1 and 2 of the study if any of the following criteria are met:

1. Prior treatment with a PARP inhibitor.
2. Current treatment with a CDK4/6 inhibitor or endocrine therapy other than anastrozole, letrozole, exemestane, and tamoxifen, with or without ovarian suppression.
3. Participants have any sign of metastasis or local recurrence after comprehensive assessment conducted per protocol.
4. Participants have shown no definitive response to preoperative chemotherapy by pathologic, radiological, or clinical evaluation, in cases where preoperative chemotherapy was administered (see Appendix 1).
5. Participants have systolic BP >140 mmHg or diastolic BP >90 mmHg that has not been adequately treated or controlled.
6. Participants have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.
7. Participants have received colony-stimulating factors (eg, granulocyte macrophage colony-stimulating factor or recombinant erythropoietin) within 4 weeks prior to the first dose of study treatment.
8. Participants have previously or are currently participating in a treatment study of an investigational agent within 4 weeks of the first dose of therapy preceding the study.
9. Participants have received live vaccine within 30 days of planned start of study randomization. Study participants can be vaccinated against Corona virus disease 2019 (COVID-19) using vaccines authorized via the appropriate regulatory mechanisms (i.e. Emergency Use Authorization, Conditional Marketing Authorization or Marketing Authorization Application). Note: messenger ribonucleic acid (mRNA) and adenoviral-based COVID-19 vaccines are considered nonlive. If COVID-19 vaccine is administered at any time, the date, name of the COVID-19 vaccine anatomic location, etc. as outlined in Section 6.8, must be entered in the eCRF. Refer to Appendix 3 for further information regarding COVID-19 vaccination timing and recommendations.
10. Participants have known hypersensitivity to the components of niraparib, placebo, or their formulation excipients.
11. Participants have undergone major surgery within 4 weeks of starting the first dose of study treatment or have not recovered from any effects of any major surgery.
12. Participants have a second primary malignancy. Exceptions are the following:

- Adequately treated nonmelanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS) of the breast, Stage I Grade 1 endometrial carcinoma.
- Other solid tumors and lymphomas (without bone marrow involvement) diagnosed ≥5 years prior to randomization and treated with no evidence of disease recurrence and for whom no more than 1 line of chemotherapy was applied

13. Participants have current active pneumonitis or any history of pneumonitis requiring steroids (any dose) or immunomodulatory treatment within 90 days of planned start of the study.
14. Participants have any clinically significant concomitant disease or condition (such as transfusion-dependent anemia or thrombocytopenia) that could interfere with, or for which the treatment might interfere with, the conduct of the study or that would, in the opinion of the Investigator, pose an unacceptable risk to the participants in this study.
15. Participants have any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study requirements and/or follow-up procedures. Those conditions should be discussed with the participants before study entry.
16. Participants have high medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection (including COVID-19). Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, active uncontrolled coagulopathy, bleeding disorder, or any psychiatric disorder that prohibits obtaining informed consent.
17. Participant is pregnant, breastfeeding, or expecting to conceive children while receiving study treatment and/or for up to 180 days after the last dose of study treatment (except France, see Section 10.14.1.1).
18. Participants have presence of hepatitis B surface antigen or a positive hepatitis C antibody test result at Screening or within 3 months prior to first dose of study treatment. Participants with presence of hepatitis B core antibody should also be excluded. NOTE: Participants with chronic hepatitis B virus (HBV) infection, who meet the criteria for anti-HBV therapy may be eligible if the participant is on a suppressive antiviral therapy prior to initiation of cancer therapy.

    NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA PCR is obtained. Also, participants with a history of Hepatitis C infection may be eligible if they have both: completed curative therapy, have an HCV viral load <quantifiable limit.
19. Participant is immunocompromised. Participants with splenectomy are allowed. Participants with known human immunodeficiency virus (HIV) are allowed if they meet the following criteria:
    a. Cluster of differentiation 4 ≥350/µL and viral load <400 copies/mL

b. No history of acquired immunodeficiency syndrome-defining opportunistic infections within 12 months prior to enrollment.

c. No history of HIV-associated malignancy for the past 5 years.

d. Concurrent antiretroviral therapy as per the most current National Institutes of Health (NIH) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV [NIH, 2021] started >4 weeks prior to study enrollment.

20. Participants have a known history of MDS or AML.

5.3. Lifestyle Considerations

Not applicable for this study.

5.4. Prescreen Failures and Screen Failures

Participants will undergo prescreening followed by screening for eligibility in the study as outlined in Section 1.3 and Section 5. Prescreen failures are defined as participants who consent to participate in the clinical study but are not subsequently eligible for screening. Participants who do not meet ctDNA criteria due to insufficient tissue may submit additional tissue. Additionally, participants may be tested multiple times for the presence of ctDNA (up to 10 times over 2 years or up to 18 times over a maximum of 6 years since end of definitive therapy, depending on the cohort; see Table 2, Table 13, and Figure 3).

A screen failure occurs when a participant who consents to participate in the clinical study and successfully completes prescreening is not subsequently randomized. Individuals who meet the prescreening criteria to enter into screening but do not meet the Screening criteria for participation in this study may be rescreened. Participants should not be rescreened more than twice. Participants who are rescreened are required to sign a new ICF and should be assigned a new participant number for every Screening/Rescreening event. Rescreened participants will not be required to complete prescreening procedures. All screening criteria (with the exception of those outlined in the SOA; Table 3) are required to be repeated if they fall outside of 6 weeks prior to first dose.

Participants that were deemed prescreen failures under previous versions of the protocol due to negative ctDNA test results may have the opportunity to re-enter prescreening and be offered additional tests (as outlined in Table 2 and Figure 3) if they are within the window for testing and meet all the prescreening eligibility criteria, including but not limited to Prescreening criteria P2 and P4, once Protocol Amendment 02 is implemented. These participants must sign the prescreening ICF again. As of the date of the decision to stop enrollment, prior prescreen-fail patients (who had not already signed Protocol Amendment 02 consent), are not allowed to be re-enrolled or reconsented and no further assessments or ctDNA testing are allowed.

A minimal set of prescreen or screen failure information is required to ensure transparent reporting of prescreen or screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, prescreen or screen

failure details, eligibility criteria, disease characteristics, and prior therapy and surgeries (as per the SOA; Section 1.3), information from any previous trials with the same investigational medicinal product (IMP), any protocol deviations, and any SAEs.

6. STUDY TREATMENTS AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Study treatments to be administered in this study are summarized in Table 15 and Section 6.1.1. For further details, refer to the Pharmacy Manual and/or the product label.

6.1. Study Treatments Administered

Details about the investigational products are provided in Table 15. As of the date of the decision to stop enrollment, the study was centrally unblinded and participants in the placebo arm are to stop administration of placebo.

Table 15 Investigational Products

	Investigational Product	
Treatment name	Niraparib	Placebo
Type	Drug	Drug
Dose formulation	CCI [redacted]	
Unit dose strength		
Route of administration		
Use		
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	CCI [redacted] Each bottle will be labeled as required per country requirements.	CCI [redacted] Each bottle will be labeled as required per country requirements.
Manufacturer	GSK	GSK

Abbreviation: NA=not applicable.

6.1.1. Niraparib

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

Niraparib will be supplied as CCI [redacted]. Niraparib tablets will be packaged in high-density polyethylene bottles with child-resistant closures. Participants will be provided enough tablets to accommodate 28 days of dosing plus up to 3 days for visit flexibility.

CCI [redacted]

CCI [redacted]

Table 16 Recommended Initial Starting Dose

Hepatic Function	Baseline Criteria	Starting Dose
Normal or mildly impaired hepatic function[a]	Weight <77 kg, platelets <150,000/µL, or both	200 mg once daily (two 100-mg tablets)
	Weight ≥77 kg and platelets ≥150,000/µL	300 mg once daily (three 100-mg tablets)
Moderate hepatic impairment[b]	Weight <77 kg, platelets <150,000/µL, or both	200 mg once daily (two 100-mg tablets)
	Weight ≥77 kg and platelets ≥150,000/µL	200 mg once daily (two 100-mg tablets)

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

a. Mildly impaired hepatic function is defined as either AST >ULN and total bilirubin ≤ULN; or any AST and total bilirubin >1.0× to 1.5× ULN

b. Moderate hepatic impairment is defined as total bilirubin >1.5× and ≤3× ULN and any level of AST elevation.

Participants will be instructed to take their niraparib dose at approximately the same time each day, except on clinic visit days. On these days, participants should hold their niraparib dose until their visit; it will be taken at the site. Participants must swallow and not chew CCI [redacted] If a participant vomits or misses a dose of niraparib, a replacement dose should not be taken. Bedtime administration may be a potential method for managing nausea. Niraparib may be taken with or without food or water.

Dose adjustments are described in Section 6.4. Once initial starting dose has been assigned, dose escalation is not allowed.

The label text of the study treatments will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries**. Blinded niraparib study treatment will be provided to participants on niraparib treatment only. Open-label supplies will be provided to those participants upon transition to the PACT Phase. Participants on placebo treatment will not receive further study treatment**.

6.2. Preparation, Handling, Storage, and Accountability

Preparation

The **Pharmacy Manual** contains instructions for administration as well as complete instructions for collection, processing, shipping, and handling. A pharmacist, Investigator, or designee will dispense study treatment for each participant according to the protocol and the **Pharmacy Manual.**

Handling and Storage (Including Disposal)

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants randomized in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. Precaution will be taken to avoid direct contact with the study treatment. A Material Safety Data Sheet describing occupational hazards and recommended handling precautions will be provided to the Investigator. In the case of unintentional occupational exposure, notify the monitor, GSK Medical Monitor, and/or GSK study contact.
4. At the end of the study, when all participants have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification in order to allow drug destruction or return procedure. After receiving Sponsor approval in writing, the investigational site is responsible for destruction of study treatment according to local regulations. If a site does not have the capability for onsite destruction, the Sponsor will provide a return for destruction service through a third party. Both the unused and expired study treatment must be destroyed, upon authorization of the Sponsor, according to local regulations and procedures, and a copy of the destruction form must be filed in the study binder.
5. The treatment provided for this study is to be used only as indicated in this protocol and only for the participants entered in this study.
6. Further guidance and information for the final disposition of unused study treatment are provided in the **Pharmacy Manual.**

Accountability

1. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
2. Details of maintaining drug accountability, including information on the accountability log, will be provided in the **Pharmacy Manual.**

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

All participants will be centrally randomized using CCI [redacted] of the date of the decision to stop enrollment, no additional randomizations were approved by the sponsor.

In Cohort 1, participants with confirmed detectable ctDNA and confirmation of t*BRCA*mut status will be randomized 1:1 to either niraparib or placebo.

In Cohort 2, participants with confirmed detectable ctDNA and confirmation of t*BRCA*wt status or with undetermined t*BRCA* status will be randomized 1:1 to either niraparib or placebo.

6.3.2. Stratification

In Cohort 1, randomization of participants will be stratified based on the following factors:

- Time from last intervention to randomization (<6 months versus ≥6 months). Time of last intervention is defined as the date of most recent oncological surgery, date of last adjuvant chemotherapy, or date of last radiotherapy fraction, whichever occurred later.
- HR status (positive versus negative)
- Prognostic Stage of breast cancer (Stage I/II versus Stage III) (Appendix 13)

In Cohort 2, randomization of participants will be stratified based on the following factors:

- Time from last intervention to randomization (<6 months versus ≥6 months). Time of last intervention is defined as the date of most recent oncological surgery, date of last adjuvant chemotherapy, or date of last radiotherapy fraction, whichever occurred later.
- Prior use of adjuvant capecitabine (yes versus no)
- Prognostic Stage of breast cancer (Stage I/II versus Stage III) (Appendix 13)

6.3.3. Blinding and Breaking the Blind

As of the date of the decision to stop enrollment, the study was centrally unblinded to allow participants on active treatment to have the option to continue treatment with niraparib if considered in the participants best interest by the Investigator, and properly documented. Administration of placebo must be stopped for participants in the placebo arm.

The identity of the treatments will be concealed by the use of study treatments that are all identical in appearance, packaging, labeling, and schedule of administration.

The participant, Investigator, blinded study staff, and the blinded Sponsor study team and its representatives will be blinded to the participant's assigned treatment from the time of

randomization until database lock. For participants who are ongoing on treatment at the end of the study, the study blind may be lifted to enable continuation of niraparib treatment, if needed. Study treatment assignment will be available to the Investigator upon request for post-study treatment planning.

If an individual's role on the study requires information about treatment assignment (eg, an individual is involved in emergency unblinding), procedures will be used to ensure all other personnel remain blinded.

In the event unblinding has occurred, the circumstances necessitating unblinding (ie, date and details about the situation leading to unblinding) must be documented promptly, and the Sponsor Medical Monitor notified as soon as possible. Only the Principal Investigator or delegate should be unblinded to the respective participant's code. Study site personnel and Sponsor personnel directly associated with the conduct of the study should not be unblinded. In the event of inadvertent participant unblinding, the participant must discontinue study intervention, but would be offered the option to continue receiving niraparib (if applicable) using another vehicle, if available.

GSK's Global Clinical Safety and Pharmacovigilance staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to the Investigators in accordance with local regulations and/or GSK policy.

6.4. Planned Dose Adjustments

6.4.1. Dose Levels and Dose Adjustment

To manage adverse reactions, Investigators may consider interruption of treatment, dose reduction, or discontinuation, consistent with the following guidance. The severity of AEs will be graded utilizing the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), Version 5.0. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Table 17, Table 18, and Table 19. Participants who are on treatment with niraparib/placebo, as well as standard of care therapies such as endocrine therapy in Cohort 1 or concurrent adjuvant pembrolizumab therapy, should have decisions regarding dose interruptions/reductions of niraparib/placebo and standard of care therapies made independently, according to investigator-assessed causality.

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Once a dose is reduced, the participant must remain at the reduced dose for the study; even if the AE resolves, the dose should not be re-escalated.

Table 17 Niraparib/Placebo Dose Reduction for Adverse Reactions

Dose Level	Initial Dose: 300 mg/day	Initial Dose: 200 mg/day
Starting dose	300 mg/day (three 100-mg tablets)	200 mg/day (two 100-mg tablets)
First dose reduction	200 mg/day (two 100-mg tablets)	100 mg/day (one 100-mg tablet)
Second dose reduction	100 mg/day (one 100-mg tablet)	NA or discontinuation of niraparib

Abbreviation: NA=not applicable.

Table 18 Dose Modifications for Nonhematologic Adverse Reactions

Nonhematologic NCI-CTCAE Grade ≥3 adverse reaction where prophylaxis is not considered feasible or adverse reaction event persists despite treatment	Withhold niraparib/placebo until resolution of adverse reaction and/or for a maximum of 28 days. Resume niraparib/placebo at a reduced dose per Table 17.
NCI CTCAE Grade ≥3 treatment-related adverse reaction event lasting more than 28 days while the participant is administered niraparib/placebo 100 mg/day	Discontinue medication.

Abbreviation: NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 19 Dose Modifications for Hematologic Adverse Reactions

Weekly blood draws for CBC will be monitored until the adverse reaction resolves, and to ensure the safety of the new dose, weekly blood draws for CBC will also be required for an additional 4 weeks after the adverse reaction has been resolved to the specified levels, after which monitoring every 4 weeks may resume.	
Platelet count <100,000/µL	First occurrence: • Withhold niraparib/placebo for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. • Resume niraparib/placebo at the same or reduced dose per Table 17. • If nadir platelet count was <75,000/µL, resume at a reduced dose after recovery.
	Second or third occurrence: • Withhold niraparib/placebo for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. • Resume niraparib/placebo at a reduced dose per Table 17. • Discontinue niraparib/placebo if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period or if the participant has already undergone dose reduction to CCI g once daily.[a]

Neutrophil <1,000/µL or Hemoglobin <8 g/dL	• Withhold niraparib/placebo for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1,500/µL or hemoglobin returns to ≥9 g/dL. • Resume niraparib/placebo at a reduced dose per Table 17. • Discontinue niraparib/placebo if neutrophil or hemoglobin level has not returned to acceptable levels within 28 days of the dose interruption period, or if the participant has already undergone dose reduction to CCI mg once daily.[a]
Hematologic adverse reaction requiring RBC and/or platelet transfusion	• For participants with platelet count ≤10,000/µL, platelet transfusion should be considered. If there are other risk factors such as coadministration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. • RBC transfusion is at the discretion of the Investigator. • Resume niraparib/placebo at a reduced dose.

Abbreviations: AML=acute myeloid leukemia; CBC=complete blood count; MDS=myelodysplastic syndrome; RBC=red blood cell.
[a] If MDS/AML is confirmed, discontinue niraparib/placebo.

6.5. Study Treatment Compliance

When participants self-administer study treatment at home, compliance with niraparib will be assessed by counting returned CCI during the site visits and will be documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of niraparib dispensed to and administered by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions, will also be recorded.

6.6. Treatment of Overdose

For this study, a dose of niraparib/placebo greater than indicated in this protocol within the specified administration window will be considered an overdose.

The Investigator should contact the GSK Medical Monitor immediately upon learning of an overdose and should do the following:

1. Closely monitor the participant for AE/SAE and laboratory abnormalities.
2. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF. **Refer to Section 10.8.**

Decisions regarding overdose management, monitoring duration, dose interruptions, or dose modifications will be made by the Investigator in consultation with the GSK Medical Monitor based on the clinical evaluation of the participant.

6.7. Treatment After the End of the Study

At the time of study closure, participants who are experiencing therapeutic benefit from treatment and an acceptable tolerability profile may have the option to continue treatment with niraparib after the end of the study. For those participants that may continue receiving niraparib after the end of the study, they may continue to be followed for safety until disease progression, unacceptable toxicity, initiation of new anticancer therapy, withdrawal of consent, or discontinuation for any other reason.

As of the date of the decision to stop enrollment, upon discontinuation from assigned study treatment, participants may receive additional (non-protocol) therapy at the discretion of the treating physician. For participants who discontinue study treatment, any poststudy intervention will not be provided as part of the protocol unless otherwise specified in Section 1.3 (Table 4, Table 5, and Table 6).

The Investigator is responsible for ensuring that consideration has been given to the poststudy care of the participant's medical condition, whether or not GSK is providing specific poststudy treatment.

The EOS is defined as the date of the last visit of the last participant in the study or last scheduled procedure for the last participant in the study.

6.7.1. Continued Access to Study Intervention

Participants receiving study treatment (niraparib) at the time of the final analysis DCO date may continue to receive niraparib if, in the opinion of their treating physician, they are benefiting from continued treatment, and they do not meet any protocol-defined treatment discontinuation criteria (Section 7). Niraparib will continue until a discontinuation criterion, as assessed by the Investigator, has been met.

Participants who continue niraparib in the PACT Phase will be cared for in accordance with local standard clinical practice at a participant's particular site, in addition to surveillance scans.

Participants will continue to be monitored for all SAEs, AEs leading to treatment discontinuation, overdoses, and pregnancy and AESIs while receiving niraparib. With the exception of SAEs, AEs leading to treatment discontinuation, overdoses and pregnancy cases and AESIs that must continue to be reported to GSK, information relating to participant care will be recorded on participant medical records and will not otherwise be reported for the purposes of this study. Investigators must continue to report all SAEs, AESIs, AEs leading to treatment discontinuation, overdose and pregnancy reports until 30 days after the participant's last dose of study treatment in accordance with Section 10.8.

Post final analysis DCO date, reporting and follow up of SAEs, AESIs, AEs leading to discontinuation, overdose and pregnancy reports will be done via paper forms (or alternative reporting method as indicated by Sponsor, should one become available) (see Section 10.9, Section 10.10, and Section 10.11 for details). For dispensing of niraparib and maintaining niraparib accountability in the PACT Phase, please refer to Section 6, as well as the Pharmacy Manual. Surveillance scans for disease

progression and/or recurrence will be provided per protocol. All other assessments will revert to standard of care at their site.

Note: All SAEs assessed as related by the Investigator must continue to be reported for all study participants until study close out. All AESIs, regardless of causality, must continue to be reported for all study participants until death or loss to follow up.

Participants currently in prescreening for ctDNA testing must have their final ctDNA test drawn prior to DCO and will not be eligible to continue on study once DCO is reached. After DCO is reached, participants eligible for surveillance scans (i.e., participants randomized to placebo and participants who were ctDNA+ve prior to date of decision to stop enrollment), as outlined in Table 12, may continue receiving surveillance scans until disease progression and/or recurrence or a stopping criterion is met as listed in Section 7.

6.8. Concomitant Medications and Nondrug Therapies

Participants should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate.

Participants will be instructed to inform the Investigator prior to starting any new medications from the time of first dose of study treatment until the Safety Follow-up Visit occurring 30 days after end of study treatment. Any concomitant medication(s), including nonprescription medication(s) and herbal product(s), taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior anticancer therapies will be recorded in the eCRF. Past and current endocrine therapies, ovarian suppressive agents, antiresorptive therapies such as bisphosphonates or denosumab, and pembrolizumab should be recorded in the study database.

The COVID vaccine given at any time should be recorded as a concomitant medication; the date of vaccination, name of the vaccine, dose number (1st/2nd/booster injection), injection site (anatomic location), and injection side (laterality) must be entered into the eCRF. Refer to Appendix 3 for further information regarding COVID-19 vaccination timing and recommendations.

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

6.8.1. Prohibited Medications and Nondrug Therapies

Known prior medications that exclude a participant from participating in the study are described in the exclusion criteria (Section 5.2).

Participants are prohibited from receiving the following therapies during the Screening and Treatment Periods of this study:

- Systemic anticancer or anticancer biological therapy; however, biological therapy for the treatment of COVID-19 and other non-oncologic conditions is permitted. Concurrent endocrine therapy is permitted, if indicated. Concurrent adjuvant pembrolizumab is permitted, if clinically indicated, and as specified in the Schedule of Activities (Table 2 footnote a, Table 3, and see Figure 1).
- Chemotherapy.
- Investigational agents other than niraparib.
- Prophylactic cytokines (eg, granulocyte colony-stimulating factor) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to local guidelines.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in this clinical study.
  An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with niraparib are unknown; therefore, live virus and bacterial vaccines should not be administered to participants in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. Study participants can be vaccinated against COVID-19 as outlined in Section 5.1 and Section 6.8. Intranasal influenza vaccines (eg, FluMist) are live attenuated vaccines and are not allowed.

The niraparib safety profile includes risk for thrombocytopenia; therefore, participants should be advised to use caution when taking anticoagulants (eg, warfarin) and antiplatelet drugs (eg, aspirin). In addition, given the reported small risk of thrombocytopenia with non-mRNA-based COVID-19 vaccinations, whenever possible, a 28-day window should be allowed between administration of non-mRNA COVID-19 vaccination and initiation of niraparib therapy.

Even though inhibition of CYP3A4 in the liver is not expected, the potential to inhibit CYP3A4 at the intestinal level has not been established at relevant niraparib concentrations. Therefore, caution is recommended when niraparib is combined with active substances the metabolism of which is CYP3A4-dependent and, notably, those having a narrow therapeutic range (eg, ciclosporin, tacrolimus, alfentanil, ergotamine, pimozide, quetiapine, and halofantrine).

Neither niraparib nor the primary circulating metabolite, M1, is a CYP3A4 inducer in vitro. In vitro, niraparib weakly induces CYP1A2 at high concentrations, and the clinical relevance of this effect could not be completely ruled out. M1 is not a CYP1A2 inducer. Therefore, caution is recommended when niraparib is combined with active substances the metabolism of which is CYP1A2-dependent and, notably, those having a narrow therapeutic range (eg, clozapine, theophylline, and ropinirole).

Niraparib is not an inhibitor of bile salt export pump (BSEP). In vitro, niraparib inhibits P-glycoprotein (P-gp) very weakly and breast cancer resistance protein (BCRP) with a half-maximal inhibitory concentration (IC_{50})=161 µM and 5.8 µM, respectively. Therefore, a clinically meaningful interaction related to an inhibition of these efflux transporters, although unlikely, cannot be excluded. Caution is then recommended when niraparib is combined with substrates of BCRP (eg, irinotecan, rosuvastatin, simvastatin, atorvastatin, and methotrexate).

Niraparib is an inhibitor of multidrug and toxin extrusion protein (MATE)1 and -2 with IC_{50} of 0.18 µM and ≤0.14 µM, respectively. Increased plasma concentrations of co-administered medicinal products that are substrates of these transporters (eg, metformin) cannot be excluded.

In vitro, niraparib weakly inhibits the organic cation transporter 1 (OCT1) with an IC_{50}=34.4 µM. Caution is recommended when niraparib is combined with active substances that undergo an uptake transport by OCT1 such as metformin.

Physicians should follow the current versions of the niraparib IB for information on the general management of participants.

6.8.2. Other Study Restrictions

Participants who are blood donors should not donate blood during the study and for 90 days after the last dose of study treatment.

Participants should maintain a normal diet, unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 5.

7.1. Withdrawal/Stopping Criteria

Participants will continue to receive their assigned treatment **or assigned assessments (e.g., participants not on study treatment and receiving surveillance scans)** until disease recurrence as assessed by RECIST v1.1, death, withdrawal of consent, loss to follow-up, or until unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 7.1.1. Note that disease recurrence excludes all in situ cancer events (see Section 8.3.1). Those participants who have completed 39 cycles (approximately 3 years) with no evidence of recurrence will have the option to either continue treatment or stop treatment at that time.

In addition, study treatment may be permanently discontinued for any of the following reasons, unless otherwise specified below:

- AE
  - If a participant has any treatment-related NCI-CTCAE v5.0 Grade 3 or 4 AEs (see Table 19 on separate guidelines for platelet count) that have not reverted to NCI-CTCAE v5.0 Grade 1 or better within 28 days of dose interruption.
  - If upon re-challenge with study treatment at the lowest allowable dose any NCI-CTCAE v5.0 Grade 3 or 4 AEs recur, the participant must be discontinued from niraparib treatment.
- Must be permanently discontinued for MDS or AML
- Additional primary malignancy other than MDS or AML may require discontinuation. To be assessed by the treating physician in agreement with the Sponsor.
- Must be permanently discontinued for Posterior Reversible Encephalopathy Syndrome (PRES)
- Risk to the participant as judged by the Investigator, Sponsor, or both
- Severe noncompliance with protocol as judged by the Investigator, Sponsor, or both.
- Must be permanently discontinued for pregnancy.
- Must be permanently discontinued for withdrawn consent.
- Inadvertent participant unblinding
- Lost to follow-up.
- Study is closed or terminated.

If a participant with any of the above criteria is allowed to continue study treatment, the Investigator must contact the GSK Medical Monitor.

The primary reason that study treatment was permanently discontinued must be documented in the participant's medical records and eCRF.

If the participant voluntarily discontinues from treatment due to toxicity, "adverse event (AE)" will be recorded as the primary reason for permanent discontinuation on the eCRF.

Once a participant has permanently discontinued from study treatment, the participant will not be allowed to be re-treated on study but would be offered the option to continue receiving niraparib (if applicable).

All participants must be followed for survival, up to the end of study as defined in this protocol. Discontinuation of study intervention does not impact participation in the study.

Participants who discontinue from study treatment will continue to receive follow-up assessments as specified in the Schedule of Activities (Table 3) and described in Section 4.1, and data collection should continue.

If the participant does not agree to continue in-person visits during the follow-up period, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the participant, contact with a relative or treating physician, or collecting information from medical records. The approach taken should be recorded in the medical records. A participant who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Under Protocol Amendment 03, on the date of the decision to stop enrollment, all randomization to study treatment is discontinued. All participants on study are centrally unblinded and those on placebo will stop the study intervention immediately, as outlined in Table 6. Participants on niraparib may continue treatment until disease recurrence at the discretion of the Investigator if they are deriving benefit from treatment. Participants will be managed as outlined in Table 11. Participants discontinued from study intervention will have follow-up assessments as outlined in Table 6. See Table 5 for end of study assessments for participants that are ctDNA+ and not yet randomized.

Following PACT implementation, all recruited participants who no longer receive study treatment, should be managed as per Section 6.7.1.

7.1.1. Liver Chemistry Stopping Criteria

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

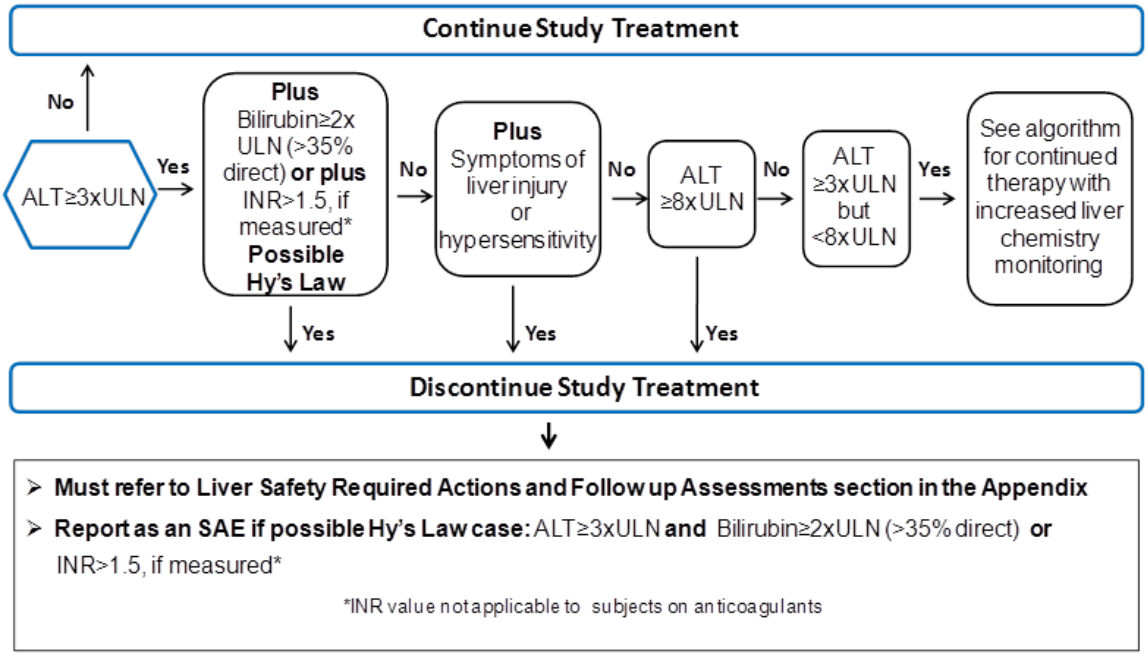
Discontinuation of study treatment for abnormal liver tests is required when the following occurs:

- A participant meets one of the conditions outlined in the Liver Chemistry Stopping and Increased Monitoring Algorithms (Figure 4 and Figure 5)

  OR

- In the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the Investigator believes that it is in the best interest of the participant.

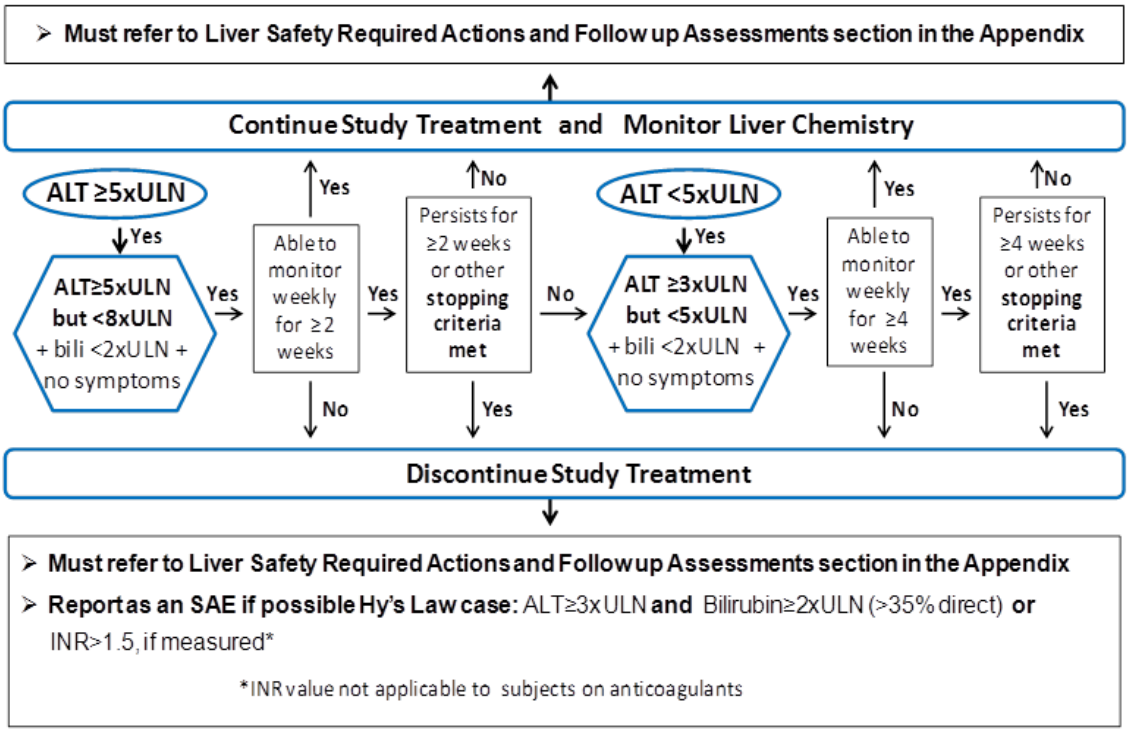
Figure 4 Liver Chemistry Stopping and Increased Monitoring Algorithm for Participants with Entry Criteria ALT ≤2.5×ULN



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

The Liver Safety Required Actions and Follow-up Assessments section can be found in Appendix 6.

Figure 5 Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3×ULN but <8×ULN for Participants with Entry Criteria ALT ≤2.5×ULN



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

The Liver Safety Required Actions and Follow-up Assessments section can be found in Appendix 6.

7.1.1.1. Restart/Rechallenge After Liver Stopping Criteria Met

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

- GSK Medical Governance approval is granted.

  AND

- Ethics and/or Institutional Review Board (IRB) approval is obtained, if required.

  AND

- Separate consent for treatment restart/rechallenge is signed by the participant, and the participant is informed of any associated risks.
- Refer to Appendix 6 for details on the restart/rechallenge process.

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

7.2. Participant Discontinuation/Withdrawal from the Study

Specific reasons for discontinuing from the study include the following:

- Withdrawal of consent by the participant, who is at any time free to discontinue participation in the study, without prejudice to further treatment
- Lost to follow-up
- Death from any cause
- Sponsor's decision to terminate study
- Investigator's decision

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

Documentation of participant consent for Further Biomedical Research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed. If a participant withdraws from the study, he/she may request destruction of samples taken and not tested, and the Investigator must document this in the site study records. Terms and conditions for participant withdrawal will be fully detailed in the ICF.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

As of the date of the decision to stop enrollment, participants found to be on placebo must stop study intervention immediately. Participants deriving benefit from niraparib, as determined by the Investigator, will continue to receive treatment until disease recurrence. For participants randomized onto the study, participants will be considered to have completed the study when they have completed their last study procedure (as outlined in Section 1.3).

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible,

3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

7.3.1. Further Biomedical Research Maintaining Confidential Participant Information

The Sponsor will conduct Further Biomedical Research on specimens and data collected during this study. This research may include genetic and genomic analyses, gene expression profiling, proteomics, metabolomics, and the measurement of other analytes after the study is completed. It may also include analysis of histological and/or clinical images and data. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from properly consented participants and per local regulations.

In an effort to optimize the research that can be conducted with Further Biomedical Research specimens, it is essential to link the study participant's clinical study data with Further Biomedical Research test results. The clinical study data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, treatment type, and treatment outcomes are critical to understanding the clinical context of Further Biomedical Research analytical results.

To maintain privacy of information collected from specimens obtained for Further Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E15 guidelines, Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories [ICH E15, 2007].

At the clinical study site, unique codes will be placed on the Further Biomedical Research specimens for transfer to the storage facility. This first code is a random number that does not contain any personally identifying information embedded within it in order to maintain participant privacy. The link (or key) between participant identifiers and this first unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

Participants may withdraw their consent for Further Biomedical Research and have their specimens and all derivatives destroyed. Participants may withdraw consent at any time by contacting the Investigator.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. General Guidelines

- Study procedures and their timing are summarized in the Schedule of Activities (Table 3). As a result of the decision to permanently stop enrollment, assessments are discontinued as outlined in Section 1.3 and assessments for participants in Prescreening, Screening, or randomized onto the ZEST study as of the date of the decision to stop enrollment are outlined in Table 4, Table 5, and Table 6.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed by the Investigator and/or site study team to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for Screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the SOA.
- Results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1.1. General Guidance for Treatment Continuity When Participants Are Unable to Come into the Clinic

As of the date of the decision to stop enrollment, at-home nursing services will no longer be offered.

Due to the significant challenges that currently face the healthcare system and participants due to COVID-19 as well as the potential for enduring or additional quarantine measures or other unforeseen circumstances, the following guidance is being provided in this protocol. In the spirit of global diversity in the COVID-19 pandemic and its impact on healthcare in each individual country as well as the recently issued guidance by several regulatory authorities, the autonomy of each investigative site to assess the benefit/risk for their participants participating in the niraparib clinical studies should be maintained.

Prior to utilization of any of the measures outlined in this section, discussion and approval must be obtained from the Sponsor/contract research organization (CRO).

It is expected that sites participating in niraparib clinical studies will make every effort to ensure proper monitoring and well-being of enrolled participants by adhering to safety monitoring as outlined in the protocol SOA. The use of local laboratories/clinics and local radiology centers or of home nursing to reduce the need for the participant to come into the hospital are supported, if deemed necessary for the well-being of the participant. These local facilities should be added to regulatory documents, as required. Utilization of home nursing should be as follows:

The Sponsor has retained an in-home nursing vendor to provide aspects of a traditional site visit in the participant's own home, allowing for consistency, continuity, and quality of care throughout the study when a participant may be unable to travel. This service can be utilized for participants who do not wish to travel to the study site or if it was determined not to be in the best interest of the participant to report to the study site.

If sites opt to utilize this service, they must inform the participant that the service will be provided their name, address, and telephone number. Participants must also be told that this information will not be shared with the Sponsor. This conversation must be documented in the source documents. An ICF addendum describing this process is available for use, dependent on local regulations.

The home nursing service may perform the following functions:

- Measurement of vital signs
- Collection of PK samples
- Local hematology and central laboratory assessment sample collection, including blood, as outlined in Table 20 (for Germany, see Table 30)
- Submission to the participant's site for processing and analysis of laboratory assessments
- Processing and submission of the central laboratory assessment to appropriate vendors
- Review/documentation of AEs, SAEs, concomitant medications, and questionnaires to supplement the Investigator.
- Completion of visit documentation

Additionally, regulatory guidance issued in response to the COVID-19 pandemic supports the use of central and remote monitoring programs to maintain oversight of clinical sites. Any restrictions in place at the site that will impact monitoring and/or participant access to the site and care providers should be communicated to the Sponsor and CRO.

The following are general rules for participants with limited possibility to travel (see Table 20; for Germany, see Table 30)

- If possible, replace in-person visits with phone contact or alternative location for assessment, such as local laboratories, clinics, and imaging centers.

- In instances where it is desired to reduce participant exposure in clinic, in-person visits every other cycle are acceptable if there are no ongoing AEs or new AEs. At this time, these missed visits will be considered protocol deviations.
- Delay in oral niraparib/placebo treatment for up to 28 days is acceptable if the participants do not have access to local laboratories and whereby the site's pharmacy will not dispense the study treatment unless participant is cleared with laboratory tests by the Principal Investigator per the institution's standard operating procedure (SOP).
  - If an interruption longer than 28 days is required, contact the GSK Medical Monitor around Day 28 of interruption. This will be reviewed, and recommendations will be made on a case-by-case basis.
- Drug dispensation for niraparib/placebo is possible for multiple cycles, with a maximum of 2 bottles dispensed at once to participants who have not experienced an SAE related to the study treatment within the last 3 months (=no ongoing "related" SAE).

Table 20 Required Data Collection and Safety Precautions for At-Home Nursing Visits

Assessment	Recommendation
Follow-up assessment	Contact participant by phone. This discussion should include assessment of new therapies and overall survival.
Hematology	Assessments may be performed through at-home nursing or at local laboratory. Arrangements for at-home nursing or the use of a local laboratory should be made by the site including the reporting of results to the PI for review.
Vital signs	Assessments may be performed through at-home nursing or at local laboratory or clinic. Arrangements for at-home nursing or the use of a local laboratory/clinic should be made by the site including the reporting of results to the PI for review.
Adverse events	• Ongoing AEs and SAEs – reviewed by phone • If hematologic AE are ongoing, a local CBC is desirable • New AEs/SAEs – may be assessed by phone (please remember to submit SAE documentation within 24 hours of learning of the event) **(For Germany, see Section 10.14.2)**
Concomitant medications	Reviewed by phone and via medical record review
PK	Blood samples for PK may be collected through at-home nursing. Arrangements for at-home nursing should be made by the site.

Abbreviations: AE=adverse event; CBC=complete blood count; CT=computed tomography; ctDNA=circulating tumor DNA; EC=Ethics Committee; IRB=Institutional Review Board; MRI=magnetic resonance imaging; PI=Principal Investigator; PK=pharmacokinetic; PRO=patient-reported outcome; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event.
As of the date of the decision to stop enrollment, at-home nursing services will no longer be offered.

8.1.1.1. Direct to Participant Investigational Medicinal Product Shipments

IRB/Ethics Committee approvals must be obtained as required by local requirements prior to shipping IMP (ie, niraparib/placebo) directly to participants.

If sites opt to utilize delivery of niraparib/placebo from the clinical site to the participant's home, they must inform the participant that a courier will be provided their name, address, and phone number to deliver the medication. They must also be told that this information will not be shared with the Sponsor. This conversation must be documented in source documents.

The courier has mitigations for sites that are not allowing external vendors into the clinics; the Sponsor/CRO must be informed of any site-specific barriers so that adequate arrangements can be made prior to shipment of any materials.

For sites that do not wish to utilize the GSK courier service, the following requirements must be met:

- The site must provide either the SOP outlining the transportation process, if available, or documentation of site transport policies for GSK/CRO review.
- Once the site SOP and/or documentation of site procedures has been reviewed and approved by GSK/CRO, the site may transport niraparib/placebo per their institutional standards. At a minimum, sites must adhere to the following guidelines when transporting niraparib/placebo:

– The primary packing container must be packed in a way that will maintain a temperature of 15°C to 30°C.*

– A temperature monitor must be included with the shipment and placed next to the primary packing container.

– The temperature monitor must be able to record maximum/minimum temperature as well as the duration. If the temperature monitor cannot record this information, the site must record time and temperature at which it was stored prior to transport as well as time and temperature at conclusion of transport on the Investigational Product Transfer Log for external transport. **

Sites receiving the transported investigational product must record if the alarm is triggered on the monitor on the Investigational Product Transfer Log and file in the pharmacy binder to be reviewed during Independent Drug Monitoring Visits (IDMVs). **

Sites must complete the Investigational Product Transfer Log (or equivalent) for each transfer instance, which will be maintained in the pharmacy binder for review during IDMVs.

Sites must report any temperature excursions of the investigational product as soon as identified. Please refer to the In-transit Temperature Excursion section of the **Pharmacy Manual** for instructions on how to proceed if a temperature excursion occurs. If no alarm, the monitors can be discarded. **

*Validated Shipper must meet International Safe Transit Association 7e or 7d certified qualification.

**We ask that sites use a courier who can check the temperature monitoring device upon receipt at the participant's home and report back the results to the site. If this is not feasible, the participants should be instructed not to dose until the site can contact the participant by phone and confirm that the investigational product shipment was received in good condition and stayed within the limits of the temperature monitor. This follow-up must be documented in the participant's source notes.

8.2. Screening and Baseline Assessments

8.2.1. Baseline Assessments at Screening

Refer to the SOA (Table 3) for the full list of assessments collected during Screening. Prior to entering the Screening Period, it must be confirmed in Prescreening (Table 2) that participants have detectable ctDNA (see Section 8.8), and all submitted prescreening tissue samples are of adequate quality per central review. For participants on study as of the date of the decision to stop enrollment, please refer to Table 4, Table 5, and Table 6 for Prescreening and Screening assessments.

Tumor characteristics to be collected during Screening include, but are not limited to, histologic tumor type, tumor grade, tumor stage (clinical prognostic, pathologic prognostic, and/or anatomic staging as per the AJCC 8th edition [Hortobagyi, 2007]; also see Appendix 13), and response to neoadjuvant chemotherapy (as applicable). Primary pathology reports will be collected from biopsy and all surgical resections characterizing ER status (with percent or Allred score, if available), PgR (with percent or Allred score, if available), and HER2 status (with immunohistochemistry and in situ hybridization, if available), as well as tumor grade.

The stage of breast cancer at Baseline will be determined as follows:

- Baseline staging for participants who received neoadjuvant treatment prior to surgery will be based on pretreatment clinical prognostic staging, per AJCC for breast cancer staging criteria 8th edition (Appendix 13), as assessed by the Investigator based on radiological and/or clinical assessment.
- Baseline staging for participants who underwent initial surgery and did not receive neoadjuvant treatment will be based on post-surgical pathological prognostic staging (see Appendix 13), per AJCC for breast cancer staging criteria 8th edition,-as assessed by the Investigator based on pathologic assessment.

8.2.2. Baseline CT/MRI and Bone Scan

An IV contrast-enhanced-CT scan of the chest, abdomen, and pelvis (preferred imaging method) and a bone scan will be conducted within 42 days (6 weeks) prior to randomization (as outlined in Table 3; as of the date of the decision to stop enrollment, please refer to Table 5 or Table 6 for assessment details for ctDNA+ participants remaining on study). An IV contrast-enhanced MRI of the abdomen and pelvis plus noncontrast CT of the chest should only be conducted if clinically indicated (eg, if

participant is sensitive to IV CT contrast or shortage of contrast). If brain metastasis is suspected, IV contrast-enhanced MRI is preferred over IV contrast-enhanced CT for imaging of the brain. The same imaging modality, method, and anatomical coverage should be used throughout the study.

8.3. Efficacy Assessments

8.3.1. Postbaseline Imaging and Tumor Assessment

The efficacy of study treatment will be evaluated by assessment of disease recurrence by the Investigator using RECIST v.1.1 (Appendix 3) [Eisenhauer, 2009]. As of the date of the decision to stop enrollment, refer to Table 6 for frequency/timing of assessments for randomized participants, on study at the time of implementation of the amendment. **Central review of scans is discontinued, and scans do not need to be sent to the central imaging vendor.**

- Disease assessment modalities may include imaging (eg, CT scan, MRI), physical examination (as indicated for palpable/superficial lesions), and histopathology. Bone scans should only be performed postbaseline if clinically indicated. If brain metastasis is suspected, IV contrast-enhanced MRI is preferred over IV contrast-enhanced CT for imaging of the brain.
- Postbaseline disease assessments are scheduled every 12 weeks (84±7 days) from the date of randomization for the first 2 years and every 24 weeks (168±7 days) thereafter, or more frequently as clinically indicated (unscheduled), until the Investigator's assessment of disease recurrence using RECIST v1.1 (Table 3). The date of disease recurrence will be the earliest date that recurrence is assessed by the Investigator, whether by radiology or histopathology. Radiological assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.
- It is important to adhere to the imaging schedule. If scans are performed outside of the specified window interval and the participant has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points.
- All radiological images/scans at the time points specified in Table 3, as well as any unscheduled images/scans, must be submitted (preferably electronically) to a central imaging vendor for quality control, storage, and analysis by blinded independent central review (BICR). As of the date of the decision to stop enrollment, central review of scans is discontinued and scans do not need to be sent to the central imaging vendor. Analysis by BICR is no longer applicable.
- For postbaseline assessments, a window of ±7 days is permitted to allow for flexible scheduling.
- If an equivocal new lesion is observed on a postbaseline radiological assessment, a follow-up scan should be acquired at least 4 weeks later to reassess. On the follow-up scan, if the equivocal new lesion becomes unequivocal, the date of progression is the date of the scan when the new

lesion first appeared (refer to Appendix 3). Any lesion assessed by the Investigator as representative of metastatic disease should be biopsied if possible to document disease recurrence histologically. In the event that disease recurrence occurs without any radiologic correlate, the date of disease recurrence is the date of biopsy with histopathologic confirmation of recurrent breast cancer.

- For this study, disease recurrence will exclude all in situ cancer events (ipsilateral or contralateral DCIS, ipsilateral or contralateral lobular carcinoma in situ [LCIS], and all in situ cancers of nonbreast sites).
- If a participant discontinues study treatment for any reason other than disease recurrence per RECIST v1.1, death, withdrawal of consent, or loss to follow-up, then scans and ctDNA sample collection should continue at the specified intervals until disease recurrence is confirmed per RECIST v1.1.
- In the case of contralateral invasive breast cancer, ipsilateral or contralateral DCIS, or second primary nonbreast invasive cancer, scans and ctDNA sample collection will continue until participants meet the criteria for DFS (as defined in Section 8.3.2).
- To ensure comparability between the baseline and subsequent radiological assessments, the same method of assessment and the same technique should be used throughout the study.

8.3.2. Exploratory Efficacy Endpoint: Disease-Free Survival

As of the date of the decision to stop enrollment, DFS is being evaluated as an exploratory endpoint.

DFS as the exploratory endpoint is defined as the time until disease recurrence, measured from the time of randomization to the earliest date of assessment of disease recurrence or death by any cause. Disease recurrence will be assessed by the Investigator using RECIST v1.1.

The definition of DFS used in this study is same as the definition of recurrence-free survival used in Hudis et al [Hudis, 2007]. DFS events includes the following:

- Ipsilateral invasive breast tumor recurrence (IIBTR): invasive breast cancer involving the same breast parenchyma as the original primary.
- Regional invasive breast cancer recurrence: invasive breast cancer in the axilla, regional lymph nodes (including ipsilateral axillary, ipsilateral infraclavicular, ipsilateral internal mammary, and ipsilateral supraclavicular nodes), chest wall, and skin of the ipsilateral breast.
- Distant recurrence: metastatic disease - breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.
- Death attributable to any cause, including breast cancer, nonbreast cancer, or unknown cause.

For this study, disease recurrence will exclude all in situ cancer events (ipsilateral or contralateral DCIS, ipsilateral or contralateral LCIS and all in situ cancers of nonbreast sites).

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8.3.3. Exploratory Efficacy Endpoint: Distant Recurrence-Free Survival

DRFS as an exploratory endpoint in this study will be evaluated based on the Investigator's assessment using RECIST v1.1 and is defined as the time from randomization to the first detection of distant metastasis or death by any cause.

DRFS events include the following:

- Distant recurrence: metastatic disease - breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.
- Death attributable to any cause, including breast cancer, nonbreast cancer, or unknown cause.

8.3.4. Exploratory Efficacy Endpoint: Time to First Subsequent Therapy

Time to first subsequent therapy (TFST) is defined as the time from randomization to the date of the first anticancer therapy used subsequent to the date of the endpoint DFS or death by any cause.

Anticancer therapy includes systemic therapy, radiation therapy, or surgical intervention.

8.3.5. Exploratory Efficacy Endpoint: Time to First Subsequent Chemotherapy

Time to first subsequent chemotherapy is defined as the time from randomization to the date of the first systemic chemotherapy used subsequent to the date of the endpoint DFS or death by any cause.

8.3.6. Exploratory Efficacy Endpoint: Time to Symptomatic Progression

Time to symptomatic progression is defined as the time from randomization to the date of symptomatic progression, which either coincides with or is subsequent to the date of the endpoint DFS. Symptomatic progression includes any of the following:

- Development of a skeletal-related event: pathologic fracture, spinal cord compression, or need for surgical intervention or radiation therapy (including palliative radiotherapy) to the bone
- Initiation of a new systemic anticancer therapy for cancer pain progression or worsening of disease-related symptoms
- Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy

8.3.7. Exploratory Efficacy Endpoint: Invasive Disease-Free Survival

IDFS will be assessed per the definition included in STEEP 2.0 [Tolaney, 2021] (Table 21), which defines IDFS as including the following events:

- IIBTR: invasive breast cancer involving the same breast parenchyma as the original primary.
- Regional invasive breast cancer recurrence: invasive breast cancer in the axilla, regional lymph nodes (including ipsilateral axillary, ipsilateral

infraclavicular, ipsilateral internal mammary, and ipsilateral supraclavicular nodes), chest wall, and skin of the ipsilateral breast.

- Distant recurrence: metastatic disease - breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.
- Death attributable to any cause, including breast cancer, nonbreast cancer, or unknown cause.
- Contralateral invasive breast cancer.
- Second primary nonbreast invasive cancer.

IDFS specifically excludes all in situ cancer events (ipsilateral or contralateral DCIS, ipsilateral or contralateral LCIS, and all in situ cancers of nonbreast sites).

8.3.8. Exploratory Efficacy Endpoint: Invasive Breast Cancer-Free Survival

- IBCFS will be assessed per the definition included in STEEP 2.0 [Tolaney, 2021] (Table 21), which defines IBCFS as including the following events:
- IIBTR: invasive breast cancer involving the same breast parenchyma as the original primary.
- Regional invasive breast cancer recurrence: invasive breast cancer in the axilla, regional lymph nodes (including ipsilateral axillary, ipsilateral infraclavicular, ipsilateral internal mammary, and ipsilateral supraclavicular nodes), chest wall, and skin of the ipsilateral breast.
- Distant recurrence: metastatic disease - breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.
- Death attributable to any cause, including breast cancer, nonbreast cancer, or unknown cause.
- Contralateral invasive breast cancer.

IBCFS specifically excludes all in situ cancer events (ipsilateral or contralateral DCIS, ipsilateral or contralateral LCIS, and all in situ cancers of nonbreast sites).

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8.4. Safety Assessments

Planned timepoints for all safety assessments for Cohort 1 (t*BRCA*mut/HER2−) and Cohort 2 (t*BRCA*wt/TNBC) are presented in Table 3. As of the date of the decision to stop enrollment, refer to Table 6 for frequency/timing of safety assessments for randomized participants on study. Safety assessments for participants in Prescreening and Screening as of the date of the decision to stop enrollment are outlined in Table 4 and Table 5.

8.4.1. Physical Examinations

A full physical examination will include assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (at Screening only) and weight will also be measured and recorded. Full physical examinations will be conducted at Screening.

Symptom-directed physical examinations will include assessments based on participants' current symptoms and will be performed at subsequent visits as summarized in Table 3.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.4.2. ECOG Performance Status

Performance status will be assessed using the ECOG performance status scale (Appendix 7) as specified in Table 3. The same observer should assess performance status each time, if possible.

8.4.3. Vital Signs

Vital sign measurements are recommended to be measured after remaining seated for 5 to 10 minutes. Vital sign measurements will include temperature, systolic and diastolic BP, heart rate (pulse), and respiratory rate. Vital signs will be assessed at designated study visits as specified in Table 3.

If participants are unable to attend the clinic visits on Cycle 1/Day 1 (postdose), Cycle 1/Day 15, and Cycle 2/Day 1 (postdose), they must have assessments for these visits performed through at-home nursing on the date the visit would have occurred. If participants are unable to attend clinic visits on Cycle 1/Day 8, Cycle 1/Day 22, Cycle 2/Day 8, Cycle 2/Day 15, and Cycle 2/Day 22, they may have the assessments for these visits performed either through a local laboratory/clinic or through at-home nursing on the date the visit would have occurred. As of the date of the decision to stop enrollment, at-home nursing services will no longer be offered.

Three readings of BP and pulse rate are recommended. In cases where 3 readings are taken, the first reading should be rejected and the second and third readings averaged to get the measurement to be recorded in the eCRF.

Vital signs will be measured more frequently if warranted by the clinical condition of the participant. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

8.4.4. Electrocardiograms

Participants will undergo 12-lead electrocardiogram (ECG) at Screening as specified in Table 3. Participants will be supine and rested for approximately 2 minutes before ECGs are recorded.

8.4.5. Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and the SOA (Table 3) for the timing and frequency of these tests. All protocol-required laboratory tests must be conducted in accordance with the Study Laboratory Manual. Clinical laboratory assessments will be performed by the local laboratory at the investigational site. If allowed by country regulation/ethics, clinical safety laboratory sampling may be conducted remotely in-home nursing services. As of the date of the decision to stop enrollment, at-home nursing services will no longer be offered.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal/baseline or are no longer considered significantly abnormal by the Investigator or GSK Medical Monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor should be notified.

If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

Hematologic, blood chemistry, and coagulation factor testing may occur more frequently than is specified in the SOA, if medically indicated per the Investigator's judgment or if the event meets the criteria for study treatment dose modification (see Section 6.4). Additional tests may be performed at a laboratory facility other than the study site, but the test results must be reported to the study site, the study site must keep a copy of test results with the participant's study file, and the results must be entered into the eCRF.

Any suspected case of MDS/AML reported while a participant is receiving treatment or followed for post-treatment assessments must be referred for evaluation to a local hematologist to perform bone marrow aspirate and biopsy as per local practice. The study

site must receive a copy of the hematologist's report of aspirate/biopsy findings, which must include a classification according to the World Health Organization, and other sample testing reports related to MDS/AML. Report data will be entered in the appropriate eCRF pages, and the site must keep a copy of all reports with the participant's study file. If a diagnosis of MDS/AML is confirmed by a hematologist, the participant must permanently discontinue study treatment.

Any suspected case of secondary cancer (new malignancies other than MDS/AML) reported while a participant is receiving treatment or followed for post-treatment assessments must be investigated, including obtaining and documenting a histological diagnosis. Testing completed as part of standard of care is sufficient as long as the methods are deemed acceptable after consultation with the GSK Medical Monitor.

8.4.6. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing study entry criteria.
- Pregnancy testing (serum or highly sensitive urine pregnancy test) must be conducted for WOCBP within 72 hours prior to the first dose of study treatment and then, starting in Cycle 2, within 72 hours of Day 1 of every cycle for the duration of the Treatment Period. Test results must be available and negative before the first dose of study treatment.
- Additional serum or highly sensitive urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
- Any pregnancies that occur within 180 days (for France, see Section 10.14.1.1) post-treatment are to be reported as described in Section 8.5.5.

8.5. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs, SAEs, and other safety events can be found in Appendix 8. AESIs are defined in Section 8.5.8.

AEs will be reported by the participant (or, when appropriate, by a caregiver, or surrogate).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all events.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 8.

8.5.1. Time Period and Frequency for Collecting AE and SAE Information

- Reporting of safety events is to begin at the time of ctDNA Prescreening ICF signature date only for events related to ctDNA and WES blood sample collection procedures (Table 2).
- All AEs and SAEs will be collected and recorded for each participant from the day of signing the main study ICF until 30 days after last dose of study treatment or the start of new anticancer therapy, as shown in the SOA (Table 3). However, any SAEs assessed as related to study participation (eg, study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to niraparib will be recorded from the time a participant consents to participate in the study until study closeout as specified in the SOA.
- All AESIs, regardless of causality, will be collected and reported from the signing of the main study ICF until study closeout at the time points specified in the SOA and as described in Section 8.5.8.
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent for the main study will be recorded as medical history/current medical conditions and not as AEs.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 8. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available. (For Germany, see Section 10.14.2.2.)
- Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.
- **For participants in PACT Phase, SAEs, AESIs, AEs leading to treatment discontinuation, overdose and pregnancy reports including follow-up reports will continue to be reported directly to GSK via paper forms (or alternative reporting method as indicated by Sponsor, should one become available) through 30 days after last dose of study. See Section 10.8, Section 10.9, Section 10.10, and Section 10.11 for details.**
- **All SAEs assessed as related by the Investigator continue to be reported for all participants (not only participants in PACT Phase) until study close out and all AESIs, regardless of causality, continue to be reported for all participants (not only participants in PACT Phase) until death or loss to follow up.**
- **Additionally, any SAEs that are ongoing at the time of the final DCO must be followed up to resolution unless the event is considered by the Investigator unlikely to resolve, or the patient is lost to follow-up or dies.**

GSK retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at EOS, if judged necessary.

8.5.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be followed until the event is resolved, stabilized, otherwise explained, the participant is lost to follow-up (as defined in Section 7.3), or until the participant has died. Further information on follow-up procedures is given in Appendix 8.

8.5.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/Independent Ethics Committees (IECs), and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.5.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants who receive study treatment will be collected after the start of study treatment and until 180 days after the last dose of study treatment in female participants and 90 days after the last dose of study treatment for female partners of male participants. (For France, see Section 10.14.1.1.)
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the pregnancy of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female

partner). While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.5.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partners, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

8.5.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 8 and all deaths, whether or not they are considered SAEs, specific Cardiovascular and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

The cardiovascular-related eCRFs are presented as queries in response to reporting of certain cardiovascular Medical Dictionary for Regulatory Activities (MedDRA) terms. The cardiovascular information should be recorded in the specific cardiovascular section of the eCRF within 1 week of receipt of a cardiovascular event data query prompting its completion.

The death-related eCRF is available at all times under Common Forms and should be completed within 1 week of when the death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

For death unequivocally due to disease under study, record death in the Death eCRF. For death due to reasons other than the disease under study, record death in the Death eCRF and Death Details eCRF as outlined in the eCRF completion guidelines.

8.5.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event that is part of the natural course of the disease under study (ie, disease recurrence or hospitalization due to disease recurrence) does not need to be reported as an SAE. Death due to disease under study is to be recorded on the Death eCRF.

8.5.8. Adverse Events of Special Interest

An AESI is any AE (serious or nonserious) that is of scientific and medical concern specific to niraparib for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is warranted. These events must be recorded as such on the eCRF. Serious AESIs must be reported to the Sponsor within 24 hours of the Investigator becoming aware of them. **(For Germany, see Section 10.14.2.2.)**

The AESIs for niraparib are as follows:

- MDS and AML
- Second primary cancers (new malignancies other than MDS or AML)

These AESIs for niraparib should be reported to the Sponsor until death or loss to follow-up.

8.6. Pharmacokinetics

As of the date of the decision to stop enrollment, collection of blood samples for PK analysis and the PK substudy are discontinued.

For all participants in Cohort 1 and Cohort 2, sparse blood samples will be collected to characterize niraparib exposure in participants with breast cancer and to explore the relationship between exposure to niraparib and responses in efficacy and safety. Blood samples will be collected predose (up to 60 minutes prior to dosing) and 3 hours postdose (±15 minutes) at Cycle 1/Day 1, Cycle 1/Day 15, and Cycle 2/Day 1 and predose (up to 60 minutes prior to dosing) at Cycle 4/Day 1 and Cycle 8/Day 1, as specified in Table 7. If participants are routinely taking their niraparib/placebo dose in the evening, they must be instructed to transition to niraparib/placebo morning dosing 1 week before the PK sampling day. If participants are unable to attend the clinic visits on Cycle 1/Day 1 (postdose), Cycle 1/Day 15, and Cycle 2/Day 1 (postdose), these visits may be performed through at-home nursing (see Section 8.1.1) at which blood samples for PK will be collected on the date the visit would have occurred.

A subset of participants in Cohort 1 will have additional blood samples collected in a PK substudy. The PK substudy will include at least the first 40 randomized participants receiving endocrine therapy in Cohort 1 at sites participating in the PK substudy. The samples collected in the PK substudy will be analyzed to characterize the steady-state PK of endocrine therapy and to assess any potential effect of niraparib on endocrine therapy exposure, as data permit. Based on the randomized nature of the study, it is assumed that approximately 20 participants in the PK substudy will be receiving endocrine therapy with niraparib, while the remaining participants will be receiving endocrine therapy with placebo, allowing for a comparison of endocrine therapy PK with or without niraparib co-administration. Additional participants may be included in the PK substudy if there are too few participants receiving any of the individual endocrine therapies to meet the objectives of the substudy; if feasible, 6 participants per endocrine therapy will be targeted.

Blood samples will be collected from participants in the PK substudy predose (up to 60 minutes prior to dosing) and 1, 2, 4, 6, and 8 hours postdose on Cycle 1/Day 15 for the analysis of anastrozole, letrozole, exemestane, tamoxifen, endoxifen, and N-desmethyl

tamoxifen (N-DMT) and niraparib, as appropriate. These time points were selected based on the PK properties of the endocrine therapies and the length of time it takes to reach niraparib steady state, allowing for the parameters' minimum plasma concentration at steady state ($C_{min,ss}$), maximum plasma concentration at steady state ($C_{max,ss}$), and area under the plasma concentration-time curve over the dosing interval at steady state (AUC_{ss}) to be determined reliably for the endocrine therapies and niraparib.

Participants in the PK substudy who vomit after taking their study treatment on a PK sampling day will need to return another time for their PK assessments.

On the PK sampling day, participants should withhold both the endocrine therapy and niraparib/placebo dose until the predose PK sample has been taken. At the clinic, niraparib/placebo should be administered first, and the endocrine therapy should be administered immediately after (within 5 minutes) to align with the sampling scheme. Participants must be instructed to dose study treatment and endocrine therapy in the morning for 1 and 2 weeks, respectively before PK sampling on Cycle 1/Day 15 (as outlined in Table 8).

A blood sample for measuring niraparib concentration may be collected for a liver event [see Appendix 6].

Samples may be analyzed for the relevant analyte using validated analytical methods. Samples collected from participants randomized to niraparib treatment will be analyzed for niraparib concentrations using a validated liquid chromatography-tandem mass spectrometry method.

For all PK samples, instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for analyses of niraparib plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these blood samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Treatment concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.7. Genetics

See Section 10.12 for information regarding the use/analysis of DNA including for WES testing. Details on processes for collection and shipment and destruction of these samples can be found in the Study Laboratory Manual.

8.8. Translational Research

Translational research may include research using DNA derived from tumor tissue or blood (see Section 10.12). All participants will undergo ctDNA Prescreening, utilizing the Signatera test for ctDNA. For the Signatera test, all participants must provide an archival tumor tissue specimen of the primary tumor, including pathology reports for all tumor tissue samples. Tissue sample requirements are outlined in the Study Reference Manual. For participants in both Cohorts 1 and 2, a blood sample is also required for

WES, and subsequent blood samples for the ctDNA testing will be collected according to the schedule summarized in Table 2 and according to the schedule shown in the SOA (Table 3) during the Treatment Period. As of the date of the decision to stop enrollment, refer to Section 1.3, and Table 4, Table 5, and Table 6 for changes to ctDNA testing for participants in Prescreening, Screening, and/or randomized onto the ZEST study.

During ctDNA Prescreening, tumor tissue samples from all participants will be collected for confirmatory central t*BRCA* testing using the CCI [redacted]. Participants with HR+/HER2− breast cancer must have a known and documented t*BRCA*mut to qualify for ctDNA Prescreening. All participants, including those with TNBC, will have their t*BRCA* status confirmed by a central laboratory prior to randomization. Note that the confirmatory central t*BRCA* test does not distinguish between somatic and germline *BRCA* mutations and does not replace standard germline testing.

Participants in Cohort 2 will have the HRD status of their tumor determined by CCI [redacted]. Incidental non-*BRCA* tumor mutation findings will be released to the Investigator as recommended per NCCN Guidelines [NCCN, 2021].

Participants are required to have ctDNA testing performed predose on Cycle 1/Day 1 and then every 12 weeks (84±7 days) from randomization until disease recurrence, as specified in the SOA (Table 3).

If a participant discontinues study treatment for any reason other than disease recurrence per RECIST v1.1, death, withdrawal of consent, or loss to follow-up, then ctDNA sample collection should continue at the specified intervals until disease recurrence is confirmed.

Exploratory biomarker analysis to identify factors important for niraparib therapy may be pursued. Blood samples for exploratory biomarker testing will be collected at the time points specified in the SOA (Table 3). CCI [redacted]

For participants who experience disease recurrence, an optional tumor tissue sample at the time of recurrence is also highly encouraged.

All samples will be collected and managed centrally, when possible, and distributed either directly or subsequently to designated translational research laboratories for biomarker testing. Details on tissue and blood sample collection, processing, storage, shipping, and handling instructions can be found in the Study Laboratory Manual.

Remaining tumor tissue samples and tumor-derived samples such as DNA and remaining blood and/or blood-derived samples such as plasma and DNA may be stored for potential further biomarker testing in cancer-related research and may be used for the development of companion diagnostic tests.

8.8.1. Tumor Tissue Collection at Time of Disease Recurrence

Data from these investigations may contribute to the understanding of the tumor microenvironment, including, but not limited to, tumor characteristics and gene and

protein expression and how they relate to niraparib clinical activity. Research biopsies at the time of disease recurrence are optional and apply only to those participants who are planning to undergo a biopsy of a visceral site (ie, nonbony lesion) as part of standard clinical care. Biopsies must be performed prior to initiating new anticancer therapy (see Table 3). It is preferred that for tumor biopsies that are not simply incisional or excisional, a 16-gauge core biopsy needle is used; however, a smaller bore needle may be used if considered necessary for the participant's safety. Four core needle biopsies need to be obtained. Fine needle biopsies are not recommended for this study. It is recommended that participants undergoing tumor biopsy have a prothrombin time/activated partial thromboplastin time <1.5 × ULN. Details regarding tumor tissue sample collection and management are provided in the Study Laboratory Manual.

As of the date of the decision to stop enrollment, collection of tumor tissue at time of disease recurrence is discontinued.

8.9. Patient-Reported Outcome Measures

PROs (including the 30-question EORTC-QLQ-C30, 6-question EQ-5D-3L, single-item PGIS/PGIC, and FACT-GP5, as well as a subset of approximately 15 questions from the PRO-CTCAE) will be used to measure the patient-reported assessment of treatment throughout study participation as specified in the SOA (Table 3). Summaries of each PRO instrument are provided below.

PRO questionnaires should be collected prior to dosing or clinical procedures during the Treatment Period on the assigned clinic visit day. After the Treatment Period, PRO assessments are conducted at the EOT Visit, the Safety Follow-up Visit, and the first 2 Post-treatment Follow-up assessments. They may be administered by telephone during follow-up if the participant is no longer actively returning to the site.

The questionnaires will be administered to participants in different regions based on the availability of translated versions.

Participants will be instructed on the completion of the questionnaires by site personnel who have been trained on their implementation.

As of the date of the decision to stop enrollment, collection of PROs is discontinued.

8.9.1. EORTC-QLQ-C30

The change from baseline in EORTC-QLQ-C30 will be assessed as a secondary endpoint. The EORTC-QLQ-C30 was developed to assess the quality of life of patients with cancer, and it is the most widely used cancer-specific health-related quality-of-life (HRQoL) instrument.

The EORTC-QLQ-C30 is a 30-item questionnaire used to measure HRQoL in participants with cancer; it has been translated and validated in over 100 languages and has been used in more than 3,000 studies worldwide (http://groups.eortc.be/qol/eortc-qlq-c30). The EORTC-QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales (Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, and Social functioning), 3 symptom scales (Fatigue, Nausea and vomiting, and Pain), 6 single items (Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea, and Financial difficulties), and a global health

status/HRQoL scale. The EORTC-QLQ-C30 uses a 1-week recall period for all items and a 4-point scale for the functional and symptom scales/items with response categories of "Not at all," "A little," "Quite a bit," and "Very much." The 2 items assessing global health status/quality of life utilize a 7-point scale ranging from 1 ("Very Poor") to 7 ("Excellent") [Aaronson, 1993].

8.9.2. PRO-CTCAE

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

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

- Dry mouth
- Mouth or throat sores
- Problems with tasting food or drink
- Abdominal pain
- Cough
- Palpitations
- Rash
- Numbness or tingling in hands or feet
- Dizziness
- Headache
- Aching muscles
- Aching joints

8.9.3. FACT-GP5

The change from baseline in the FACT-GP5 will be assessed as a secondary endpoint. The Functional Assessment of Cancer Therapy - General (FACT-G) (now in Version 4) is a 27-item compilation of general questions divided into 4 primary quality-of-life domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being [Cella, 1993]. It is considered appropriate for use with participants with any form of cancer and has also been used and validated in other

chronic illness conditions (eg, HIV/AIDS and multiple sclerosis) and in the general population (using a slightly modified version).

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

8.9.4. EuroQol Questionnaire (EQ-5D-3L)

The change from baseline in EQ-5D-3L will be assessed as an exploratory endpoint. The EQ-5D-3L is a standardized instrument for use as a measure of health utility. It is designed for self-completion or interview administration and is cognitively simple, taking only a few minutes to complete.

The EQ-5D-3L self-assessment questionnaire has 2 parts. The first part consists of 5 items covering 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a 3-point Likert scale (no problems, some or moderate problems, and unable or extreme problems). Participants are asked to choose 1 level that reflects their "own health state today" for each of the 5 dimensions. Participants can be then classified into 1 of 243 distinct health states. The second part is a 20-cm visual analogue scale (EQ-VAS) that has endpoints labelled "best imaginable health state" and "worst imaginable health state" anchored at 100 and 0, respectively.

The EQ-5D-3L will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years. The EQ-5D-3L will be completed by participants last after completing all other PRO assessments.

8.9.5. Patient Global Impression Items

PGIS and PGIC will be assessed as exploratory endpoints. The PGIS assesses global impression of symptom severity at baseline and subsequent time points. The second question, the PGIC, serves to rate the global change in symptoms at subsequent time points as outlined in Table 3. In addition to evaluating symptom severity and change, these questions serve as anchors to establish thresholds of clinically meaningful change for the questionnaires in the study [Guy, 1976].

9. STATISTICAL CONSIDERATIONS

As of the date of the decision to permanently stop enrollment into the study, specific assessments such as collection of survival follow-up data, subsequent treatments, PRO data, etc. will no longer be required (as outlined in Section 1.3). Safety and tolerability of niraparib are being assessed as the primary endpoint and will use the SAF Population. Estimands are not applicable. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the SAP and final study report.

9.1. Statistical Hypotheses

As of the date of the decision to stop enrollment, there is no formal hypothesis testing framework being implemented in this study.

9.2. Sample Size Determination

The sample size determinations were based on the original ZEST study design and endpoints. A total of 40 participants were randomized in the study.

The placebo median DFS is expected to be approximately 9 months from randomization. This is based on the published data from 49 patients with primary breast cancer monitored longitudinally using serial plasma for up to 4 years after surgery and adjuvant chemotherapy [Coombes, 2019]. Plasma ctDNA was detected ahead of clinical or radiological relapse (disease recurrence) in 16 of the 18 relapsed patients. The median time from detection of ctDNA presence to disease recurrence was 8.9 months.

The placebo median OS is expected to be approximately 30 months from randomization. This is based on the estimated sum of the median DFS (9 months) and the median OS from Phase 3 studies with approved therapies in either advanced or metastatic TNBC (IMpassion130 study: 21 months [Schmid, 2018]) or advanced or metastatic g*BRCA*mut HER2− breast cancer (OlympiAD study: 19 months [Robson, 2017]; EMBRACA study: 22 months [Litton, 2018].

CCI

[redacted]

Cohort 1 (t*BRCA*mut/HER2−)

CCI

[redacted]

CCI

[redacted]

Cohort 2 (t*BRCA*wt/TNBC)

CCI

[redacted]

9.3. Data Analysis Considerations

9.3.1. Analysis Sets

The analysis populations are defined as follows:

- **ITT Population**: All participants randomized into the study. The ITT population is the primary analysis population for the efficacy analysis. For this analysis, participants will be analyzed as randomized.
- **Safety (SAF) Population**: All randomized participants who receive at least 1 dose of study treatment (niraparib or placebo). Participants will be analyzed as treated.

The ITT Population is the analysis population for the efficacy analysis. The SAF population will be the primary analysis population for the safety analyses.

Additional analysis populations may be defined in the SAP.

9.3.2. Interim Analysis

CCI

[redacted]

9.4. Key Elements of Analysis Plan

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the SAP. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the SAP and final study report.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given participant will depend on efficacy and tolerability, the duration of follow-up will vary between participants. Consequently, there will be no imputation for missing data.

Demographic and baseline characteristics will be summarized.

9.4.1. Primary Safety Analyses

The SAF Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs) will be summarized according to the scheduled nominal visit at which they were collected and across all on-treatment time points. Complete details of the safety analyses will be provided in the SAP.

9.4.1.1. Extent of Exposure

The number of participants administered study treatment will be summarized according to the duration of therapy.

9.4.1.2. Adverse Events

AEs will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the Investigator according to the NCI-CTCAE (version 5.0).

Events will be summarized by frequency and proportion of total participants, by system organ class, and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs, AEs leading to dose reduction, interruption, and/or discontinuation of study treatment, and AESIs.

AEs, if listed in the NCI-CTCAE (Version 5.0), will be summarized by maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

The incidence of deaths and the primary cause of death will be summarized.

Further details will be provided in the SAP.

9.4.1.3. Clinical Laboratory Evaluations

Clinical laboratory evaluation: The evaluation of clinical laboratory tests will focus on selected laboratory analytes from the hematology and blood chemistry panel.

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE (Version 5.0). Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criteria will be summarized using proportions.

Descriptive statistics (mean, standard deviation, median, and range) will be used to summarize change from baseline in observed value at each scheduled visit.

The worst-case toxicity grade in hematology and chemistry results during treatment will be summarized.

Further details will be provided in the SAP.

9.4.1.4. Other Safety Measures

Data for vital signs will be summarized based on predetermined criteria identified to be of potential clinical concern.

Data for physical examinations, ECOG performance status, and concomitant medications will also be summarized.

Further details will be provided in the SAP.

9.4.2. Exploratory Efficacy Analyses

The following exploratory efficacy endpoints will be evaluated:

- DFS
- DRFS

- TFST
- Time to first subsequent chemotherapy
- Time to symptomatic progression
- IDFS
- IBCFS

CCI [redacted]

9.4.3. Other Analyses

9.4.3.1. Exploratory Biomarker Analyses

CCI [redacted]

9.4.3.2. Genetic Analyses

Further details on genetic analyses will be addressed in the genetic SAP.

9.4.4. Independent Data Monitoring Committee

As of the date of the decision to stop enrollment, assessment by an IDMC is no longer needed due to study enrollment being permanently discontinued and the study being centrally unblinded.

An IDMC will be established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the participants in the study.

The IDMC will consist of 3 individuals, including 1 biostatistician and 2 physicians who are independent from the Sponsor. The membership, the key responsibilities of the IDMC, and the corresponding procedures will be defined in an IDMC Charter.

CCI [redacted]

CCI

[redacted]

10. APPENDICES

10.1. Appendix 1: Exclusion of Participants Who Have Shown No Definitive Response to Preoperative Chemotherapy

Participants who have shown no definitive response to preoperative chemotherapy by pathologic, radiological, or clinical evaluation, in cases where preoperative chemotherapy was administered, will be excluded from the study.

For study eligibility, determination of no definitive response to preoperative chemotherapy should be evaluated pathologically whenever possible.

- Radiological and/or clinical evaluation of response to preoperative chemotherapy should be used only when response cannot be determined pathologically.
- Source documentation of preoperative therapy response, including pathology reports and/or imaging reports, should be collected whenever possible.

In short, participants who demonstrate any objective sign of response to therapy by either pathologic, radiographic, or clinical assessment would be allowed to move forward with further eligibility assessment for the study.

Pathologic Evaluation

No definitive response to preoperative chemotherapy by pathologic evaluation is considered to include at least one of the following:

- CAP/AJCC System: Treatment effect in the breast: No definite response to presurgical therapy in the invasive carcinoma; or
- RCB System: RCB-III: Extensive residual disease; or
- Miller-Payne System: Grade 1: No change or some alteration to individual malignant cells, but no reduction in overall cellularity; or
- Japanese Breast Cancer Society System: Grade 0: Little change with treatment was observed in invasive cancer tissue.

If none of the above systems are routinely used at the site, other standard of care pathological assessment systems may be used to determine lack of response to postoperative chemotherapy but should be reviewed with the Medical Monitor on a case-by-case basis.

Radiological and Clinical Evaluation

If response to preoperative chemotherapy cannot be determined pathologically by the Investigator, then response should be determined radiologically and/or clinically.

No definitive response to preoperative chemotherapy by radiological and/or clinical evaluation is considered to include at least one of the following:

- Progressive disease (PD) defined as the development of new, previously undetected lesions, or an increase in the size of the primary lesion as assessed by the Investigator; or
- Stable disease (SD) defined as no decrease in size of the primary lesion, as assessed by the Investigator.

Assessment should be based on a comparison of imaging or clinical exam performed before initiation and after completion of preoperative chemotherapy.

Imaging modalities for comparison can include either mammogram, ultrasound, or magnetic resonance imaging, but the same modality must be used for both pre- and post-chemotherapy assessments.

Sources: [Fitzgibbons, 2018; Ogston, 2003; Symmans, 2007]

10.2. Appendix 2: Clinical Laboratory Tests

Screening Only Testing

The tests detailed below will be performed by the local laboratory at investigational site.

- HIV and hepatitis B and C testing performed at Screening (or within 3 months prior to first dose of study treatment) only; laboratory tests for:
  - HIV-1 and HIV-2 antibodies
  - Hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibodies
- Follicle-stimulating hormone and estradiol (in women of non-childbearing potential <60 years of age)

Continuous Laboratory Assessments

The tests detailed in Table 22 will be performed by the local laboratory at the investigational site.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or as required by local regulations.

Table 22 Protocol required Safety Laboratory Tests

Laboratory Assessment	Parameters
Hematology	• White blood cell count – total and differential • Hemoglobin • Hematocrit • Platelet count[a] • Absolute neutrophil count • Absolute lymphocyte count[f]
Coagulation factors[b]	• PT/INR • PTT/aPTT[b]

Laboratory Assessment	Parameters
Clinical chemistry[c]	• Alanine aminotransferase • Albumin[f] • Alkaline phosphatase[d] • Aspartate aminotransferase • Bilirubin (total) • Bilirubin, direct[f] • Blood urea nitrogen or urea[e,f] • Calcium[f] • Chloride[f] • CO_2 or bicarbonate[f] • Creatinine • Glucose[f] • Potassium[f] • Sodium[f] • Total protein[f]
Urinalysis	• Local standard of care urine dipsticks and/or urine laboratory parameters may be used to assess for urinary tract infection.
Pregnancy test	• Serum or highly sensitive urine hCG pregnancy test on WOCBP only.

Abbreviations: ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; BUN=blood urea nitrogen; hCG=human chorionic gonadotropin; IEC=Independent Ethics Committee; INR=international normalized ratio; IRB=Institutional Review Board; PT=prothrombin time; PTT=partial thromboplastin time; WOCBP=women of childbearing potential; ULN=upper limit of normal.

[a] Mean platelet volume is optional but encouraged, especially for participants with high-grade thrombocytopenia.

[b] Coagulation factors (PT/INR and aPTT/PTT) should be tested as part of the Screening procedures for all participants in accordance with local standard of care. Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study. If PTT/aPTT is not part of standard of care in the participant's region, then the test does not need to be performed.

[c] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 6. All events of ALT ≥3× ULN and total bilirubin ≥2× ULN (>35% direct bilirubin) or ALT ≥3× ULN and INR >1.5, if INR measured, which may indicate severe liver injury (possible Hy's law), must be reported to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

[d] If alkaline phosphatase is elevated, consider fractionating.

[e] BUN is preferred; if not available, urea may be tested.

[f] If these items are not done as part of standard of care in the participant's region, then these tests do not need to be performed. All other laboratory assessments are considered essential.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Guidelines for Assessment of Disease, Disease Progression and Response Criteria

RECIST v1.1 Assessment Guidelines [Eisenhauer, 2009]

Imaging Modality Specifications

The full Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1) guidelines [Eisenhauer, 2009] are described below; note that the outcome of interest for this study is the assessment of new lesions.

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study per participant to evaluate a tumor lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by computed tomography (CT) or magnetic resonance imaging (MRI) is required.
- Fluorodeoxyglucose (FDG)-positron emission tomography (PET) is generally not suitable for ongoing assessments of disease. However, FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed, then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the case report form (CRF).

CT and MRI: IV contrast-enhanced-CT with up to 5-mm contiguous slices is the preferred imaging modality except for imaging of the brain (IV contrast-enhanced MRI preferred). Whenever possible the same scanner should be used.

X-ray: In general, X-ray should not be used for lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered new lesions if they are clearly defined and surrounded by aerated lung; however, chest CT is preferred over chest X-ray to assess thoracic lesions.

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (ie, X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET (FDG or fluoride) may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

Guidelines for Evaluation of Disease

New Lesions

All participants in the current study have detectable circulating tumor ctDNA (ctDNA), and it is assumed that they all have tumors not yet recognizable by imaging. For disease-free survival (DFS) assessment and participant management, the protocol emphasizes specific RECIST v1.1 guidance on the appearance of new lesions. According to RECIST v1.1, the appearance of an unequivocal new lesion is required to trigger an assessment of progressive disease. The appearance of equivocal new lesions and how to deal with this with respect to identifying a date of progression is guided as follows: if an equivocal new lesion appears in the images, the Investigators are encouraged to continue treatment and to collect a follow-up scan at least 4 weeks later. If a previously equivocal new lesion coverts to an unequivocal new lesion at the follow-up scan, then the date of progression is designated by when the new lesion first appeared. Following this new lesion guidance should limit the number of premature radiological calls of progressive disease.

Evaluation of overall response

Table 23 presents the overall response at an individual time point for all possible combinations of tumor responses for participants with non-measurable only disease at baseline.

Table 23 Evaluation of Overall Response for Participants with No Evidence of Disease at Baseline

New Lesions	Overall Response
No	NED
NE	NE
Yes	PD

Abbreviations: NE=not evaluable; NED=no evidence of disease; PD=progressive disease.

Note:

- Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration.” Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.
- Overall RECIST v1.1 response options for this study will be limited to No Evidence of Disease, Not Evaluable, or Progressive Disease because participants are expected to have no radiographic evidence of disease at enrollment.

Lymphadenopathy After COVID-19 Vaccination and Tumor Assessments

Case reports of new lymphadenopathy within days to weeks after COVID-19 vaccination, local to the side of vaccine administration, have been published [Becker, 2021; Cohen, 2021; Eshet, 2021; Keshavarz, 2021]. This reactive lymphadenopathy is indistinguishable from malignant lymphadenopathy on medical images and has the potential to confound radiological tumor assessments, particularly in indications with a propensity to metastasize to local axillary lymph nodes, such as breast cancer.

Lymphadenopathy after COVID-19 vaccination is transient (appears within days and subsides within days/weeks after vaccination), local (predominantly axillary lymph node and less frequently in supraclavicular/lower cervical nodes, when administered into the deltoid muscle of upper arm), and ipsilateral to the vaccination site (e.g., right axillary lymph node if administered to right deltoid muscle). Lymphadenopathy after COVID-19 vaccination has been observed on anatomical images (CT/MRI scans) as mildly swollen (10 to 20 mm short-axis diameter) and more frequently on PET scans with elevated uptake of ^{18}F-FDG.

Vaccination information (name, date, dose number [1st/2nd/booster], injection site, and laterality) collected in the Concomitant Medications COVID-19 Vaccination eCRF will be available to site and/or central radiologists to supplement their tumor assessments.

If there is suspicion of lymphadenopathy after COVID-19 vaccination during tumor assessment, caution should be applied before classifying affected lymph nodes as unequivocal new lesions and the assignment of progressive disease. Consider imaging follow-up and/or tissue diagnosis in those recently vaccinated patients at higher risk of local malignant lymphadenopathy.

Additional COVID-19 vaccination/imaging guidance may be found in Becker et al and from the Society of Breast Imaging recommendations (SBI) [Becker, 2021; SBI, 2021]. Please contact the GSK study team for more information.

10.4. Appendix 4: Contraceptive and Barrier Guidance

Niraparib is known to have properties that require participants to use contraception. For details on niraparib, refer to the niraparib Investigator's Brochure [GSK Document Number RPS-CLIN-014110]. Based on its mechanism of action, niraparib may cause teratogenicity and/or embryo-fetal death when administered to a pregnant woman. (For France and Germany, please see Section 10.14 for Contraceptive and Barrier Guidance.)

Participants who are women of childbearing potential (WOCBP) (see WOCBP definition) may only be enrolled if they have a negative pregnancy test (serum or highly sensitive urine test) within 72 hours prior to taking study treatment. Participants must agree to abstain from activities that could result in pregnancy from Screening through 180 days after the last dose of study treatment, be willing to use a highly effective contraception (see Table 25; for Germany **Table 31**), or be considered women of non-childbearing potential (WONCBP) (see WONCBP definition).

Participants should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study. To participate in the study, they must adhere to the contraception requirements described below. If there is any question that a participant will not reliably comply with the requirements for contraception, that participant should not be enrolled in the study.

Male participants may only be enrolled if they agree to use a male condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak), or be abstinent from intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent. Male participants must use an adequate method of contraception and not donate sperm according to the timeframe in Table 24.

Table 24 Timing of Contraception and Sperm Donation[a]

Parameter	Timeframe
Contraception use, female participants	Starting with the Screening Visit through 180 days after the last dose of study treatment
Contraception use, male participants	Starting with the first dose of study treatment through 90 days after the last dose of study treatment
Sperm donation	Starting with the first dose of study treatment through 90 days after the last dose of study treatment

a. **For France, see Section 10.14.1.2; for Germany, see Section 10.14.2.2.**

Table 25 Contraceptives Allowed During the Study[c]

CONTRACEPTIVES [a] ALLOWED DURING THE STUDY INCLUDE THE FOLLOWING:
Highly Effective [b] Methods that Have Low User Dependency (*Failure rate of <1% per year when used consistently and correctly)*
• IUD (nonhormonal only)
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) – Azoospermia is a highly effective contraceptive method, provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, then an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. **Note:** Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective[b] Methods that Are User Dependent (*Failure rate of <1% per year when used consistently and correctly)*
• Sexual abstinence – Sexual abstinence is considered a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptom-thermal, and postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are **not acceptable** methods of contraception. • Barrier methods of contraception – Acceptable barrier methods of contraception include the following: male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods). The use of double-barrier methods should always be supplemented with the use of a spermicide to result in a failure rate of <1%. Female condom and male condom should not be used together.

Abbreviations: IUD=intrauterine device; WOCBP=woman of childbearing potential.

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] For Germany, see Section 10.14.2.3, Table 31.

Definition of WOCBP

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see Notes below)

Definition of WONCBP

Women in the following categories are considered WONCBP (not fertile):

1. Premenopausal female with permanent infertility due to 1 of the following (for the purpose of this study):
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy
2. Postmenopausal female

Notes:

- A postmenopausal state is defined as ≥60 years of age or <60 years of age with no menses for 12 months without an alternative medical cause.
    - Follicle-stimulating hormone (FSH) and plasma estradiol levels in the postmenopausal range should be obtained to confirm a postmenopausal state in women <60 years of age not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- For individuals with permanent infertility due to an alternate medical cause other than those previously listed, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied when determining study entry.
- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.
- Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

10.5. Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure [GSK Document Number RPS-CLIN-014110], and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

CCI [redacted]

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protect requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF
- GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about the study treatments or about the study disease; publish the results of these research efforts; and work with government agencies or insurers to have the study treatments approved for medical use or approved for payment coverage.
- The ICF contains a separate section that addresses the use of participant data and remaining samples for further research. The Investigator or authorized designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- **The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.**
- **Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.**

Committees Structure

An Independent Data Monitoring Committee (IDMC) will be established to ensure participants' safety during this study and will consist of 3 individuals, including 1 biostatistician and 2 physicians who are independent from the Sponsor. The membership, the key responsibilities of the IDMC, and the corresponding procedures will be defined in an IDMC charter.

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide all Investigators who participated in the study with a summary of the study results and will tell the Investigators what treatment their participants received. The Investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- GSK will also provide the Investigator with clinically relevant Clinical Laboratory Improvement Amendments (CLIA)-validated tumor genetic results from[CCI] test to be shared, as applicable, with their specific participants.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- GSK will provide the Investigator with the randomization codes for their site only after completion of the full statistical analysis.

- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in Case Report Form Completion Guidelines.
- Quality tolerance limits (QTLs) will be predefined in the Study Reference Manual to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during and at the end of the study, and all deviations from the QTLs and remedial actions taken will be summarized in the CSR. **As of the date of the decision to stop enrollment under Protocol Amendment 03, the study had not enrolled enough participants to define or monitor QTLs. The QTLs are no longer applicable.**
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process, including systems used, can be found in the study Data Management Plan.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 25 years from the issue of the final CSR/equivalent summary unless local regulations or institutional

policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- **Source Data Per the ICH E6 Guideline (Section 1.52) source documentation is defined as "Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."** The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- **The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.**
- **Copies of documents are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g., endpoint adjudication committee; expert reader). The non-exhaustive list of documents shared to inform the central reader may include, discharge summaries, imaging reports, ECG reports etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the Investigator sites prior to transfer. Details of the list of documents and the redaction procedure are provided in the site manual or equivalent. These documents will be used by the third party solely for the purpose indicated within this protocol.**

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study treatment development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the Investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Table 26 Liver Chemistry Stopping Criteria and Required Follow up Assessments.

Liver Chemistry Stopping Criteria –Liver Stopping Event Participant with entry criteria ALT≤2.5 × ULN	
ALT-absolute	ALT ≥8 × ULN
ALT Increase	ALT ≥5 × ULN but <8 × ULN persists for ≥2 weeks ALT ≥3 × ULN but <5 × ULN persists for ≥4 weeks
Bilirubin[a,b]	ALT ≥3 × ULN **and** bilirubin ≥ 2 × ULN (>35% direct bilirubin)
INR[b]	ALT ≥3 × ULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥5 × ULN but <8 × ULN **and** cannot be monitored weekly for ≥2 weeks ALT ≥3 × ULN but <5 × ULN **and** cannot be monitored weekly for ≥4 weeks
Symptomatic[c]	ALT ≥3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow-up Assessments following ANY Liver Stopping Event	
Actions	**Follow-up Assessments**
• Immediately discontinue study treatment • Report the event to GSK within 24 hours • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[b] • Perform liver event follow-up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below) • Do not restart/rechallenge participant with study treatment unless allowed per protocol and GSK Medical Governance approval is granted • If restart/rechallenge not allowed or not granted, permanently discontinue study treatment and may continue participant in the study for any protocol-specified follow-up assessments	• Viral hepatitis serology[d] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody.[e] • Blood sample for PK analysis, obtained within 3 hours (±15 minutes) after last dose[f] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin ≥2 × ULN • Obtain complete blood cell count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.

Required Actions and Follow-up Assessments following ANY Liver Stopping Event	
Actions	**Follow-up Assessments**
MONITORING: **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within 24 hrs • Monitor participants twice weekly until liver chemistries resolve, stabilize, or return to within baseline • A specialist or hepatology consultation is recommended **For all other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within 24 to 72 hrs • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). NOTE: Not required where test is not available per local standard-of-care • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and/or liver biopsy to evaluate liver disease[i] complete Liver Imaging and/or Liver Biopsy CRF forms.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CRF=case report form; HPLC=high-performance liquid chromatography; IgM=immunoglobulin M; INR=international normalized ratio; PCR=polymerase chain reaction; PK=pharmacokinetic; SAE=serious adverse event; ULN=upper limit of normal.

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

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

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

[d] Includes: Hepatitis A IgM antibody, hepatitis B surface antigen and hepatitis B core antibody (IgM), hepatitis C RNA, cytomegalovirus IgM antibody, Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing), and hepatitis E IgM antibody.

[e] If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].

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

Table 27 Liver Chemistry Increased Monitoring Criteria with Continued Therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
Participant <u>with</u> entry criteria ALT≤2.5 × ULN ALT ≥5 × ULN and <8 × ULN **and** bilirubin <2 × ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3 × ULN and <5 × ULN and bilirubin <2 × ULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within Baseline[a] • If at any time participant meets the liver chemistry stopping criteria, proceed as described above **For participant with entry criteria ALT≤2.5 × ULN** • If ALT decreases from ALT ≥5 × ULN and <8 × ULN to ≥3 × ULN but <5 × ULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3 × ULN and bilirubin <2 × ULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

[a] For the purpose of these guidelines, "baseline" refers to laboratory assessments performed closest and prior to first dose of study treatment.

10.7. Appendix 7: Eastern Cooperative Oncology Group Performance Status

Table 28 Eastern Cooperative Oncology Group (ECOG) Performance Status Grading

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (ie, light housework, office work).	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

Source: [Oken, 1982]

10.8. Appendix 8: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

Adverse Event (AE) Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/-SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a study participant
f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)
g. Other situations: • Possible Hy's Law case: ALT≥3×ULN AND total bilirubin ≥2×ULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE. • Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

Definition of Treatment-Emergent Adverse Event (TEAE)

TEAE Definition
• A TEAE is defined as any new AE that begins, or any pre-existing condition that worsens in severity, after at least 1 dose of study treatment has been administered.

Definition of an Adverse Event of Special Interest (AESI)

An AESI is any AE (serious or nonserious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate.

Niraparib AESIs

AESIs for niraparib are the following:

- myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML)
- second primary cancers (new malignancies [other than MDS or AML])

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information. • It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity
The Investigator will make an assessment of intensity (severity) for each AE and SAE reported during the study. The severity of AEs will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0; National Institutes of Health (NIH), National Cancer Institute (NCI). The CTCAE severity Grades 1 through 5 provide unique clinical descriptions of severity of each AE. The CTCAE v5.0 is available on the NCI/NIH website.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A *"reasonable possibility*" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- For causality assessment, the Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to GSK. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Assessment of Outcomes

The Investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

Follow-up of AEs, SAEs, AESIs, pregnancies, and any other events of interest

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information. (For reporting in Germany, see Section 10.14.2.2).
- After the initial AE/SAE/AESI/pregnancy or any other event of interest, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AESI (as defined in the Section 8.5.8), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the reporting procedures outlined for the study. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

- Furthermore, the Investigator must report any SAE occurring as a result of a post-study pregnancy that is considered by the Investigator to be reasonably related to the study intervention, to GSK as described in the section below.

Updating of SAE, AESI and pregnancy information after removal of write access to the participant's eCRF

When additional SAE, AESI or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the Investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.5.3).

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool (until DCO)

- **The primary mechanism for reporting SAE to GSK will be the electronic data collection tool until DCO is met.**
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. **
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the GSK Medical Monitor or the SAE Coordinator by telephone.
- If the site during the course of the study becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in the **local study contact document.**

** **For reporting in Germany, see Section 10.14.2.2.**

SAE/AESIs/AEs leading to treatment discontinuation/Overdose/Pregnancy Reporting to GSK via Paper Data Collection Tool/paper forms (only if electronic system unavailable and/or in PACT Phase)

- Email/Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the GSK Medical Monitor or the SAE Coordinator.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- **For PACT Phase:**
  - **SAEs/AESIs/AE leading to discontinuation/Overdose/Pregnancy reports need to be reported within 24 hours of becoming aware of the event.**
  - **Initial and follow up SAEs, AESIs, Overdose and AEs leading to discontinuation will be submitted to Sponsor on a paper SAE form.**
  - **Alternative reporting methods may become available during the PACT**

SAE/AESIs/AEs leading to treatment discontinuation/Overdose/Pregnancy Reporting to GSK via Paper Data Collection Tool/paper forms (only if electronic system unavailable and/or in PACT Phase)
Phase. Details for these methods and preferred reporting processes will be provided separately by the Sponsor, if/when applicable. • **Pregnancy cases will be submitted to Sponsor on a paper pregnancy initial or paper pregnancy follow up form.** • **In case sites need to discuss the event please contact the GSK Medical Monitor and your local CRA.** • **Details about SAE/AE reporting can be found on the paper form (Refer to Section 10.9, Section 10.9, and Section 10.11)**

10.9. Appendix 9: Pregnancy Initial Notification Form

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Protocol Identifier	Subject Identifier	Centre Number	Randomisation Number

PHARMA STUDY PREGNANCY INITIAL NOTIFICATION FORM

This form should be completed according to the protocol reporting requirements.
Note: Most protocols do not require collection of subject's partner pregnancy.
Complete this form for each subject or subject's partner who becomes pregnant during the study period. Send a copy of the form to GSK (GSK will provide separately a list of contact names and information) by mail or fax (e-mail preferred) within 24 hours of learning of the pregnancy. Once form has been completed please email to mailbox: OAX37640@GSK.com (or +44(0) 20 81814780).

Who is this form being completed for, ✓ *one:* ☐ Subject ☐ Subject's partner

MOTHER'S RELEVANT MEDICAL/FAMILY HISTORY

Mother's year of birth ☐☐☐☐ Year

Date of last menstrual period ☐☐ Day ☐☐☐ Month ☐☐ Year

Estimated date of delivery ☐☐ Day ☐☐☐ Month ☐☐ Year

Was the mother using a method of contraception? ☐ Yes ☐ No

If Yes, specify: _____

Type of conception, ✓ *one:* ☐ Normal (includes use of fertility drugs) ☐ IVF (in vitro fertilisation)

Relevant laboratory tests and procedures (e.g., ultrasound, amniocentesis and chorionic villi sampling, including dates of tests and procedures).

_____

_____

Number of previous pregnancies ☐☐ Pre-term ☐☐ Full-term

If applicable, record the number in the appropriate categories below:

☐☐ Normal births ☐☐ Spontaneous abortion
☐☐ Still births ☐☐ Elective abortion
☐☐ Children born with defects ☐☐ Other

Record details of children born with defects: _____

Are there any additional factors that may have an impact on the outcome of this pregnancy? ☐ Yes ☐ No

If Yes, specify: _____

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Protocol Identifier	Subject Identifier	Centre Number	

PHARMA STUDY PREGNANCY INITIAL NOTIFICATION FORM (Continued)

FATHER'S RELEVANT MEDICAL/FAMILY HISTORY

Only recorded if required by the protocol and Informed Consent of the father has been obtained.

(Include habitual exposures such as alcohol/substance abuse, chronic illnesses, familial birth defects/genetic/ chromosomal disorders and medication use)

_____

_____

DRUG EXPOSURES

In the following table, list all medications (including study medications) the subject received during the study period (e.g., prescription, OTC, vaccines, recreational, alcohol, etc.). Enter the investigational product details on the first line (if the investigational product is blinded, enter 'Investigational Product' on this line). If there are extensive concomitant medications, attach a copy of the Concomitant Medications CRF page.

Drug Name *(Trade Name preferred)*	Route of Admin. or For mulation	Total Daily Dose	Units	Started Pre-Study Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Medication Y=Yes N=No	Reason for Medication

Was the subject withdrawn from the study as a result of this pregnancy? ☐ Yes ☐ No

REPORTING INVESTIGATOR INFORMATION *(Forward to a more appropriate physician if needed)*

Name _____ Title __ Speciality _____

Address _____

City or State/Province _____

Country _____

Post or Zip Code _____

Telephone No _____

Fax No _____

Investigator's signature _____ Date ☐☐ ☐☐☐ ☐☐
(Confirming that the data on these pages are accurate and complete) Day Month Year

Investigator's name (print) _____

10.10. Appendix 10: Study pregnancy follow up form.

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Protocol Identifier	Subject Identifier	Centre Number	Randomisation Number

PHARMA STUDY PREGNANCY FOLLOW-UP FORM

One form should be completed per foetus (e.g., if a subject is carrying twins a form should be completed for each twin).

Who is this form being completed for, ✓ one: ☐ Subject ☐ Subject's partner

PREGNANCY STATUS

While pregnancy itself is not an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. A spontaneous abortion is always considered to be an SAE and will be reported as described in the protocol. Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the investigational product by the investigator will be reported to GSK per the protocol. Whilst the investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Early termination, ✓ *if applicable:*

☐ Stillbirth
☐ Foetal death
☐ Method used for delivery, *specify* _____

☐ Spontaneous abortion
☐ Elective abortion
☐ Other, *specify* _____

InForm studies:

- *If a female subject is pregnant and the outcomes/associated events fulfil the criteria of an SAE, complete the information in the eCRF SAE form and on this paper Pregnancy Follow-up form.*
- *If male subject's partner is pregnant and the outcomes/associated events fulfil the criteria of an SAE, then complete the information in the paper SAE form and send together with this paper Pregnancy Follow-up form.*

Paper studies: *If any of the outcomes/associated events fulfil the criteria of an SAE, complete the SAE section in the CRF.*

FOETAL/NEONATAL STATUS

☐ Normal
☐ Birth defect (i.e., structural/chromosomal disorder) *Complete Serious Adverse Event pages*
☐ Other disorder (e.g., non-structural, premature birth, intrauterine death/stillbirth)

If birth defects are diagnosed, is the origin of the defect known? ☐ Yes ☐ No

If Yes, specify

INFANT INFORMATION

Date of birth/miscarriage/termination ☐☐ ☐☐☐ ☐☐ (Day / Month / Year)

Gestational weeks at birth/miscarriage/termination ☐☐ Weeks

Infant's sex ☐ Male ☐ Female ☐ Unknown

Length ☐☐.☐ cm Weight ☐☐☐☐.☐☐ g

Apgar score (0 - 10) ☐☐ First assessment ☐☐ Second assessment

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Protocol Identifier	Subject Identifier	Centre Number	

PHARMA STUDY PREGNANCY FOLLOW-UP FORM (Continued)

ADDITIONAL DETAILS *(Provide additional details on current (abort/delivery/discharge notes etc.)*

_____

_____

_____

_____

DRUG EXPOSURES DURING PREGNANCY

Complete drug section for all drugs (including OTC/vaccines) taken by the mother during pregnancy. Do not include drugs that have already been included on the Pregnancy Notification Form.

Drug Name *(Trade Name preferred)*	**Route of Admin. or For-mulation**	**Total Daily Dose**	**Units**	**Started Pre-Study** Y=Yes N=No	**Start Date** Day Month Year	**Stop Date** Day Month Year	**Ongoing Med-ication** Y=Yes N=No	**Reason for Medication**

REPORTING INVESTIGATOR INFORMATION *(Forward to a more appropriate physician if needed)*

Name _____ Title ___ Speciality _____

Address _____

City or State/Province _____

Country _____

Post or Zip Code _____

Telephone No _____

Fax No _____

Investigator's signature _____ Date ☐☐ ☐☐☐ ☐☐
(Confirming that the data on these pages are accurate and complete) Day Month Year

Investigator's name (print) _____

10.11. Appendix 11: Serious Adverse Event (SAE) Reporting Form

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Serious Adverse Event (SAE) Reporting Form (Page 1 of 4)

INVESTIGATOR INSTRUCTIONS

SECTION 1	
What is the adverse event term?	Record one SAE diagnosis per line, or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered and the sign/symptom crossed out, initialed, and dated by the investigator. A separate form should be used for each SAE. However, if multiple SAEs which are temporally or clinically related are apparent at the time of initial reporting then these may be reported on the same page. If this was recorded previously as a non-serious event but has progressed to serious, put a line through the Non-Serious AE record and transcribe the details onto the SAE form.
What is the date and time the adverse event started?	Record the start date and time of the first occurrence of the event or signs/symptoms of the serious event, not the date and time the event became serious.
What was the outcome of this adverse event?	All SAEs must be followed until the events are resolved, the condition stabilises, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. If the SAE is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as 'Not recovered/Not resolved' or 'Recovering/Resolving'. Also enter 'Not recovered/Not resolved' if the SAE was ongoing at the time of death, but was not the cause of death, enter fatal for the SAE which was the direct cause of death.
What date and time did the adverse event end?	Record the end date. This is the date the SAE Recovered/Resolved, or if the outcome was fatal, record the date the subject died. If the event Recovered/Resolved with sequelae, enter the date the subject's medical condition resolved or stabilised. Leave blank if the SAE is 'Not recovered/Not resolved' or 'Recovering/Resolving'. Record the end time of the SAE.
What was the maximum severity/grade of the adverse event?	Record the maximum severity/grade that occurred over the duration of the event. Amend the severity/grade if it increases. Refer to the protocol for the Severity/Grade definition for the study.
Most Clinically Significant Action Taken with Study Treatment(s) as a Result of the SAE	Indicate the response to the adverse event, whether it be from the investigator, local physician not in the study, or the subject. Drug withdrawn = Administration of study treatment(s) was permanently discontinued. Dose reduced = Dose is reduced for one or more study treatment(s). Dose increased = Dose increased for one or more study treatment(s). Dose not changed = Study treatment(s) continues even though an adverse event has occurred. Drug interrupted = Administration of one or more study treatment(s) was stopped/interrupted temporarily but then restarted. Not applicable = Subject was not receiving study treatment(s) when the event occurred (e.g., pre- or post-dosing) or the subject died and there was no prior decision to discontinue Study Treatment(s).
Did the adverse event cause the subject to be discontinued from the study?	Indicate 'Yes' if the event(s) were directly responsible for the subject's withdrawal from the study, otherwise indicate 'No'.
Date/Time site was made aware of the SAE	Record Date/Time site was made aware of the SAE.
Is this event related to study treatment?	It is a regulatory requirement for investigators to assess relationship to study treatment(s) based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support 'a reasonable possibility' include, e.g., a temporal relationship, a pharmacologically predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.
Relationship to Specific Study Treatment(s)	If relationship to study treatment is Yes, specify which Study Treatment(s) caused the event.

Serious Adverse Event (SAE) Reporting Form (1.0) June 2023 Template Doc ID: TMF-15745197 Parent Doc ID: VQD-SOP- 005415

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Serious Adverse Event (SAE) Reporting Form (Page 2 of 4)

DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

SECTION 2

A serious adverse event is any untoward medical occurrence that, at any dose:

a) results in death.

b) is life-threatening.

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) requires hospitalisation or prolongation of existing hospitalisation.

Note: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is 'serious'.

When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered 'serious'. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity, or

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) is a congenital anomaly/birth defect.

f) other.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

g) possible drug-induced liver injury

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Serious Adverse Event (SAE) Reporting Form (Page 3 of 4)

INVESTIGATOR INSTRUCTIONS

SECTION 4 **If Study Treatment was Stopped, Did the Reported Event(s) Recur After Further Study Treatment(s) Were Administered?**	If deliberate or inadvertent administration of further dose(s) of study treatment(s) to the subject occurred, did the reported adverse event recur?
SECTION 9 **Details of Study Treatment(s)**	Complete this section using the information in the Study Treatment page. Details of all study treatment(s) taken until the time of the SAE should be included. Provide specific details in Section 11 Narrative Remarks if the subject has taken an overdose of study treatment(s), including whether it was accidental or intentional.

THE INVESTIGATOR MUST INFORM GSK OF SERIOUS ADVERSE EVENTS BY E-MAIL OR FAX (E-MAIL PREFERRED) WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT. ALL OF THE HEADER INFORMATION MUST BE COMPLETED BEFORE SENDING BACK TO GSK.
(The original pages must remain in the Case Report Form/Study File).

Once form has been completed, please email to mailbox:
OAX37649@GSK.com (or fax +44(0)20 8181 4780)

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Serious Adverse Event (SAE) Reporting Form (Page 4 of 4)
MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'no' box at the top of the page has been completed.
- Start dates must be provided for the reporting of serious adverse event data. If the exact date is not known, liaise with the investigator to ensure that a best estimate is provided.
- Ensure that no medical or investigational procedures are captured on Serious Adverse Events pages.
- **Death** should not be recorded as an SAE but should be recorded as the outcome of an SAE. The condition that resulted in the death should be recorded as the SAE.
- Confirm that any SAEs marked as **Recovering/Resolving** or **Not recovered/Not resolved** have been followed up for details of resolution.
- If the subject permanently discontinued study treatment due to an SAE; and will continue with early study treatment discontinuation study participation, confirm the following variables are consistent for the SAE which resulted in permanent discontinuation of study treatment:
  - Most Clinically significant Action Taken with Study Treatment(s) as a Result of the SAE on the SAE form is recorded as 'Drug Withdrawn'
  - Primary reason for study treatment discontinuation on the Study Treatment Discontinuation page is 'Adverse event.'
  - Study Conclusion page will remain blank until subject completes post early study treatment discontinuation visit(s).
- If the subject was withdrawn from the study due to an SAE, confirm the following variables are consistent for the SAE which resulted in Study Withdrawal
  - Did the adverse event cause the subject to be discontinued from the study? Should be recorded as 'Yes.'
  - Primary reason with Withdrawal on the Study Conclusion page is recorded as 'Adverse Event.'
  - Study Treatment Discontinuation form is completed with appropriate reason for study treatment discontinuation.

10.12. Appendix 12: Use/Analysis of DNA

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

10.13. Appendix 13: Breast Cancer Staging Guidance

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

American Joint Committee on Cancer (AJCC)
TNM Staging System For Breast Cancer

Primary Tumor (T) The T category of the primary tumor is defined by the same criteria regardless of whether it is based on clinical or pathological criteria, or both. The T category is based primarily on the size of the invasive component of the cancer. The maximum size of a tumor focus is used as an estimate of disease volume. The largest contiguous dimension of a tumor focus is used, and small satellite foci of noncontiguous tumor are not added to the size. The cellular fibrous reaction to invasive tumor cells is generally included in the measurement of a tumor prior to treatment; however, the dense fibrosis observed following neoadjuvant treatment is generally not included in the pathological measurement because its extent may overestimate the residual tumor volume. The clinical size of a primary tumor (T) can be measured based on clinical findings (physical examination and imaging modalities, such as mammography, ultrasound, and MR imaging) and pathological findings (gross and microscopic measurements). Clinical tumor size (cT) should be based on the clinical findings that are judged to be most accurate for a particular case, although it may still be somewhat inaccurate because the entent of some breast cancers is not always apparent with current imaging techniques and because tumors are composed of varying proportions of noninvasive and invasive disease, which these techniques are currently unable to distinguish. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification the size should be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 4.9 mm is reported as 5 mm, or a size of 2.04 cm is reported as 2.0 cm (20 mm). The exception to this rounding rule is for a breast tumor sized between 1.0 and1.4 mm. These sizes are rounded up to 2 mm, because rounding down would result in the cancer's being categorized as microinvasive carcinoma (T1mi) defined as a size of 1.0 mm or less.

Table 1. **Definitions for T, N, M**

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)*	Ductal carcinoma *in situ*
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension (round any measurement >1.0–1.9 mm to 2 mm)
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macrosopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma

*Note: Lobular carcinoma *in situ* (LCIS) is a benign entity and is removed from TNM staging in the AJCC Cancer Staging Manual, 8th Edition.

Continued

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Table 1. **Definitions for T, N, M (continued)**
Regional Lymph Nodes (N)
Clinical (cN)

cNX*	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
cN1mi**	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; *or* in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; *or* in ipsilateral internal mammary lymph node(s) with level I, II axillary lymph node metastases; *or* metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or fine needle aspiration/core needle biopsy respectively.
*The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.
**cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.

Pathologic (pN)

pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cells clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined.
pN2	Metastases in 4–9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes

Continued

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Table 1. **Definitions for T, N, M (continued)**
Pathologic (pN)

pN3	Metastases in 10 or more axillary lymph nodes; *or* in infraclavicular (level III axillary) lymph nodes; *or* positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive level I, II axillary lymph nodes; *or* in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; *or* in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); *or* metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging); *or* pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively, with NO further resection of nodes

Distant Metastasis (M)

M0	No clinical or radiographic evidence of distant metastases*
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if in non-regional nodes, metastases greater than 0.2 mm

Table 2. **AJCC Anatomic Stage Groups**

The Anatomic Stage Group table should only be used in global regions where biomarker tests are not routinely available.
Cancer registries in the U.S. must use the Clinical and Pathological Prognostic Stage Group tables for case reporting.

Stage 0	Tis	N0	M0	**Stage IIIA**	T0	N2	M0
Stage IA	T1	N0	M0		T1	N2	M0
Stage IB	T0	N1mi	M0		T2	N2	M0
	T1	N1mi	M0		T3	N1	M0
Stage IIA	T0	N1	M0		T3	N2	M0
	T1	N1	M0	**Stage IIIB**	T4	N0	M0
	T2	N0	M0		T4	N1	M0
Stage IIB	T2	N1	M0		T4	N2	M0
	T3	N0	M0	**Stage IIIC**	Any T	N3	M0
				Stage IV	Any T	Any N	M1

Notes:
1. T1 includes T1mi.
2. T0 and T1 tumors with nodal micrometastases (N1mi) are staged as Stage IB.
3. T2, T3, and T4 tumors with nodal micrometastases (N1mi) are staged using the N1 category.
4. M0 includes M0(i+).
5. The designation pM0 is not valid; any M0 is clinical.
6. If a patient presents with M1 disease prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
7. Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided the studies are performed within 4 months of diagnosis in the absence of disease progression, and provided the patient has not received neoadjuvant therapy.
8. Staging following neoadjuvant therapy is designated with "yc" or "yp" prefix to the T and N classification. There is no anatomic stage group assigned if there is a complete pathological response (pCR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

Continued

Table 2. **AJCC Anatomic Stage Groups (continued)**

Histologic Grade (G)

All invasive breast carcinomas should be assigned a histologic grade. The Nottingham combined histologic grade (Nottingham modification of the SBR grading system) is recommended and is stipulated for use by the College of American Pathologists (see www.cap.org). The grade for a tumor is determined by assessing morphologic features (tubule formation, nuclear pleomorphism, and calibrated mitotic count), assigning a value from 1 (favorable) to 3 (unfavorable) for each feature, and totaling the scores for all three categories. A combined score of 3–5 points is designated as grade 1; a combined score of 6–7 points is grade 2; a combined score of 8–9 points is grade 3. The use of subjective grading alone is discouraged.

Invasive Cancer (Scarff-Bloom-Richardson [SBR] Grading System, Nottingham Modification)

- **GX** Grade cannot be assessed
- **G1** Low combined histologic grade (favorable); SBR score of 3–5 points
- **G2** Intermediate combined histologic grade (moderately favorable); SBR score of 6–7 points
- **G3** High combined histologic grade (unfavorable); SBR score of 8–9 points

Ductal Carcinoma *in situ*: Nuclear Grade
The grade that should be used for ductal carcinoma in situ is nuclear grade (www.cap.org)

- **GX** Grade cannot be assessed
- **G1** Low nuclear grade
- **G2** Intermediate nuclear grade
- **G3** High nuclear grade

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Table 3. **Clinical Prognostic Stage**

Clinical Prognostic Stage applies to ALL patients with breast cancer for clinical classification and staging. It uses clinical tumor (T), node (N) and metastases (M) information based on history, physical examination, any imaging performed (not necessary for clinical staging) and relevant biopsies. Genomic profile information is not included in Clinical Prognostic Stage as pathologic information from surgery is necessary to ascertain the prognosis using these tools.

TNM	Grade	HER2	ER	PR	Stage
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	IB
	G2	Positive	Positive	Positive	IA
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	IB
				Negative	

TNM	Grade	HER2	ER	PR	Stage
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	IIB
			Negative	Positive	
				Negative	

Continued

*T1 includes T1mi.
**N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.

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***Table 3.* Clinical Prognostic Stage (continued)**

TNM	Grade	HER2	ER	PR	Stage
T2 N1*** M0 T3 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	
				Negative	
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	
				Negative	IIIB
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	IIIA
			Negative	Positive	
				Negative	IIIB

TNM	Grade	HER2	ER	PR	Stage
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0	G1	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	
				Negative	IIIB
	G2	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	
				Negative	IIIB
	G3	Positive	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	IIIB
			Negative	Positive	
				Negative	IIIC

Continued

*T1 includes T1mi.
***N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively.

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***Table 3.* Clinical Prognostic Stage (continued)**

TNM	Grade	HER2	ER	PR	Stage
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	IIIC
	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	IIIC
	G3	Positive	Positive	Positive	
				Negative	
			Negative	Positive	IIIB
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	IIIC
				Negative	
Any T Any N M1	Any	Any	Any	Any	IV

Notes:
1. Because N1mi categorization requires evaluation of the entire node, and cannot be assigned on the basis of an FNA or core biopsy, N1mi can only be used with Clinical Prognostic Staging when clinical staging is based on a resected lymph node in the absence of resection of the primary cancer, such as the situation where sentinel node biopsy is performed prior to receipt of neoadjuvant chemotherapy or endocrine therapy.
2. For cases with lymph node involvement with no evidence of primary tumor (e.g. T0 N1, etc.) or with breast ductal carcinoma *in situ* (e.g. Tis N1, etc.), the grade, HER2, ER, and PR information from the tumor in the lymph node should be used for assigning stage group.
3. For cases where HER2 is determined to be "equivocal" by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, the HER2 "negative" category should be used for staging in the Clinical Prognostic Stage Group.
4. The prognostic value of these Prognostic Stage Groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).

Continued

***N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively.

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Table 4. **Pathological Prognostic Stage**

Pathological Prognostic Stage applies to patients with breast cancer treated with surgery as the initial treatment. It includes all information used for clinical staging plus findings at surgery and pathological findings from surgical resection. Pathological Prognostic Stage does not apply to patients treated with systemic or radiation prior to surgical resection (neoadjuvant therapy).

TNM	Grade	HER2	ER	PR	Stage
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB

TNM	Grade	HER2	ER	PR	Stage
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
	G2	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	G3	Positive	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA

Continued

*T1 includes T1mi.
**N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.
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Table 4. **Pathological Prognostic Stage (continued)**

TNM	Grade	HER2	ER	PR	Stage
T2 N1*** M0 T3 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G2	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIA

TNM	Grade	HER2	ER	PR	Stage
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0	G1	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
	G2	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G3	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIC

Continued

*T1 Includes T1mi.
***N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively.

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Table 4. **Pathological Prognostic Stage (continued)**

TNM	Grade	HER2	ER	PR	Stage
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	
				Negative	
	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	
				Negative	IIIC
	G3	Positive	Positive	Positive	IIIB
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IIIC
				Negative	
			Negative	Positive	
				Negative	
Any T Any N M1	Any	Any	Any	Any	IV

Notes:
1. For cases with lymph node involvement with no evidence of primary tumor (e.g. T0 N1, etc.) or with breast ductal carcinoma *in situ* (e.g. Tis N1, etc.), the grade, HER2, ER and PR information from the tumor in the lymph node should be used for assigning stage group.
2. For cases where HER2 is determined to be "equivocal" by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, HER2 "negative" category should be used for staging in the Pathological Prognostic Stage Group.
3. The prognostic value of these Prognostic Stage Groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).

Table 5. **Genomic Profile for Pathologic Prognostic Staging**

When Oncotype DX Score is Less than 11...

TNM	Grade	HER2	ER	PR	Stage
T1 N0 M0 T2 N0 M0	Any	Negative	Positive	Any	IA

Notes:
1. Obtaining genomic profiles is NOT required for assigning Pathological Prognostic Stage. However genomic profiles may be performed for use in determining appropriate treatment. If the OncotypeDx® test is performed in cases with a T1N0M0 or T2N0M0 cancer that is HER2-negative and ER-positive, and the recurrence score is less than 11, the case should be assigned Pathological Prognostic Stage Group IA.
2. If OncotypeDx® is not performed, or if it is performed and the OncotypeDx® score is not available, or is 11 or greater for patients with T1–2 N0 M0 HER2–negative, ER-positive cancer, then the Prognostic Stage Group is assigned based on the anatomic and biomarker categories shown above.
3. OncotypeDx® is the only multigene panel included to classify Pathologic Prognostic Stage because prospective Level I data supports this use for patients with a score less than 11. Future updates to the staging system may include results from other multigene panels to assign cohorts of patients to Prognostic Stage Groups based on the then available evidence. Inclusion or exclusion in this staging table of a genomic profile assay is not an endorsement of any specific assay and should not limit appropriate clinical use of any genomic profile assay based on evidence available at the time of treatment.

***N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively.

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10.14. Appendix 14: Country-specific Requirements

10.14.1. France

The following sections outline France-specific changes from the main protocol.

10.14.1.1. Contraceptive Requirements

Contraception requirements were adjusted in alignment with recommendations by ANSM.

- Any pregnancies that occur within 194 days (6.5 months) post-treatment are to be reported as described in Section 8.5.5.
- Details of all pregnancies in female participants and, if indicated, female partners of male participants who receive study treatment will be collected after the start of study treatment and until 194 days (6.5 months) after the last dose of study treatment in female participants and 104 days (3.5 months) after the last dose of study treatment for female partners of male participants.

Inclusion Criteria (criteria #11 and #12)

11 A female participant is eligible if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP), as defined in Section 10.14.1.2.

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described in Section 10.14.1.2, during the Treatment Period and for at least 194 days (6.5 months) after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
- A WOCBP must have a negative pregnancy test (highly sensitive urine test or serum test as required by local regulations) within 72 hours before the first dose of study treatment.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study treatment are described in Section 8.4.6.
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

See Section 10.14.1.2 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents.

12 Male participants are eligible if they agree to the following during the Treatment Period and for at least 104 days (3.5 months) after the last dose of study treatment (see Section 10.14.1.2 for a list of acceptable birth control methods):

- Be abstinent from intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak)
  - PLUS
- Male participants must refrain from donating sperm for at least 104 days (3.5 months) after the last dose of study treatment

Exclusion Criteria (criterion #17)

17 Participant is pregnant, breastfeeding, or expecting to conceive children while receiving study treatment and/or for up to 194 days (6.5 months) after the last dose of study treatment.

10.14.1.2. Contraceptive and Barrier Guidance for France

Niraparib is known to have properties that require participants to use contraception. For details on niraparib, refer to the niraparib Investigator's Brochure. Based on its mechanism of action, niraparib may cause teratogenicity and/or embryo-fetal death when administered to a pregnant woman.

Participants who are women of childbearing potential (WOCBP) (see WOCBP definition) may only be enrolled if they have a negative pregnancy test (serum or highly sensitive urine test) within 72 hours prior to taking study treatment. Participants must agree to abstain from activities that could result in pregnancy from Screening through 194 days (6.5 months) after the last dose of study treatment, be willing to use a highly effective contraception (see Table 25), or be considered women of non-childbearing potential (WONCBP) (see WONCBP definition).

Participants should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study. To participate in the study, they must adhere to the contraception requirements described below. If there is any question that a participant will not reliably comply with the requirements for contraception, that participant should not be enrolled in the study.

Male participants may only be enrolled if they agree to use a male condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak), or be abstinent from intercourse as their

preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent. Male participants must use an adequate method of contraception and not donate sperm according to the timeframe in Table 29.

Table 29 Timing of Contraception and Sperm Donation in France

Parameter	Timeframe
Contraception use, female participants	Starting with the Screening Visit through 194 days (6.5 months) after the last dose of study treatment
Contraception use, male participants	Starting with the first dose of study treatment through 104 days (3.5 months) after the last dose of study treatment
Sperm donation	Starting with the first dose of study treatment through 104 days (3.5 months) after the last dose of study treatment

10.14.2. Germany

The following sections outline German specific changes from the main protocol regarding at-home nursing visits, SAE reporting, and contraceptive and barrier guidance. **As of the date of the decision to stop enrollment, at-home nursing services will no longer be offered.**

10.14.2.1. General Guidance for Treatment Continuity When Participants Are Unable to Come into the Clinic in Germany

Table 30 Required Data Collection and Safety Precautions for At-Home Nursing Visits in Germany

Assessment	Recommendation
Follow-up assessment	Contact participant by phone. This discussion should include assessment of new therapies and overall survival.
Hematology	Assessments may be performed through at-home nursing or at local laboratory. Arrangements for at-home nursing or the use of a local laboratory should be made by the site including the reporting of results to the PI for review.
Vital signs	Assessments may be performed through at-home nursing or at local laboratory or clinic. Arrangements for at-home nursing or the use of a local laboratory/clinic should be made by the site including the reporting of results to the PI for review.
Adverse events	• Ongoing AEs and SAEs - reviewed by phone • If hematologic AE are ongoing, a local CBC is desirable • New AEs/SAEs - may be assessed by phone (please remember to submit SAE documentation immediately when learning of the event)
Concomitant medications	Reviewed by phone and via medical record review
PK	Blood samples for PK may be collected through at-home nursing. Arrangements for at-home nursing should be made by the site.

Abbreviations: AE=adverse event; CBC=complete blood count; CT=computed tomography; ctDNA=circulating tumor DNA; EC=Ethics Committee; IRB=Institutional Review Board; MRI=magnetic resonance imaging; PI=Principal Investigator; PK=pharmacokinetic; PRO=patient-reported outcome; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event.
As of the date of the decision to stop enrollment, at-home nursing services will no longer be offered.

10.14.2.2. Time Period and Frequency for Collecting AE, AESI, and SAE Information for Germany

- All SAEs will be recorded and reported to the Sponsor or designee immediately, as indicated below. The Investigator will submit any updated SAE data to the Sponsor immediately it becomes available.

- An AESI is any AE (serious or nonserious) that is of scientific and medical concern specific to niraparib for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is warranted. These events must be recorded as such on the eCRF. Serious AESIs must be reported to the Sponsor immediately the Investigator becomes aware of them.

Follow-up of AEs, SAE, AESIs, pregnancies, and any other events of interest
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally submitted documents. • The Investigator will submit any updated SAE data to GSK immediately on receipt of the information.

Reporting of SAE to GSK (Germany)

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event immediately. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the GSK Medical Monitor or the SAE Coordinator by telephone. • If the site during the course of the study becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs. • Contacts for SAE reporting can be found in the **local study contact document.**

10.14.2.3. Contraceptive and Barrier Guidance for Germany

Table 31 Contraceptives Allowed During the Study for Germany

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE THE FOLLOWING:
Highly Effective[b] Methods that Have Low User Dependency (*Failure rate of <1% per year when used consistently and correctly)*
• IUD (nonhormonal only)
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) – Azoospermia is a highly effective contraceptive method, provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, then an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. **Note:** Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective[b] Methods that Are User Dependent (*Failure rate of <1% per year when used consistently and correctly)*
• Sexual abstinence – Sexual abstinence is considered a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptom-thermal, and postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are **not acceptable** methods of contraception.

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
[b] Failure rate of <1% per year when used consistently

10.15. Appendix 15: Abbreviations and Specialist Terms

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

Table 32 Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BER	base excision repair
BOR	best overall response
BP	blood pressure
BSEP	bile salt export pump
BRCA	breast cancer susceptibility gene
*BRCA*mut	breast cancer susceptibility gene mutation
CBC	complete blood count
CE	conformité européenne (European Conformity)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
COVID-19	Corona virus disease 2019
CR	complete response
CRO	contract research organization
CT	computed tomography
ctDNA	circulating tumor DNA
ctDNA+	ctDNA-positive
CV	Cardiovascular
CYP	cytochrome P450
DCIS	ductal carcinoma in situ
DCO	data cut-off

Abbreviation or Specialist Term	Explanation
DCR	disease control rate
DFS	disease-free survival
DoR	duration of response
DRFS	distant recurrence-free survival
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module
EOS	End of the study
EOT	End-of-Treatment
EQ-5D-3L	EuroQoL 5-Dimensional Questionnaire 3-Level Version
ER+	estrogen receptor positive
ER	estrogen receptor
E-R	exposure-response
FACT-GP5	Functional Assessment of Cancer Therapy-General Population
FDG-PET	fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
g*BRCA*mut	a deleterious or suspected deleterious germline mutation in the *BRCA* gene
GCP	Good Clinical Practice
GIS	genome instability score
H0	null hypothesis
H1	alternative hypothesis
hCG	human chorionic gonadotropin
HER2	human epidermal growth factor 2
HER2−	human epidermal growth factor 2 negative
HER2+	human epidermal growth factor 2 positive
HIV	human immunodeficiency virus
HPLC	high-performance liquid chromatography
HR	hormone receptor
HR−	hormone receptor negative
HR+	hormone receptor positive

Abbreviation or Specialist Term	Explanation
HRD	homologous recombination deficiency
HRd	homologous recombination deficient
HRp	homologous recombination proficient
HRQoL	health-related quality of life
HRR	homologous recombination repair
IB	Investigator's Brochure
IBCFS	invasive breast cancer-free survival
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICF	informed consent form
IDFS	invasive disease-free survival
IDMC	Independent Data Monitoring Committee
IDMV	Independent Drug Monitoring Visit
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IIBTR	ipsilateral invasive breast tumor recurrence
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
ISH	in situ hybridization
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
IWRS	interactive web response system
LCIS	lobular carcinoma in situ
MATE	multidrug and toxin extrusion protein
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
MRI	magnetic resonance imaging
MTM	mean tumor molecule
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events

Abbreviation or Specialist Term	Explanation
N-DMT	N-desmethyl tamoxifen
NED	no evidence of disease
NHEJ	nonhomologous end-joining
NIH	National Institutes of Health
OCT1	organic cation transporter 1
ORR	objective response rate
OS	overall survival
PACT	post-analysis continued treatment
PARP	poly(ADP-ribose) polymerase
pCR	pathological complete response
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PET	positron emission tomography
P-gp	P-glycoprotein
PgR	progesterone receptor
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PP	per protocol
PR	partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	patient-reported outcome
PRO-CTCAE	Patient-reported Outcomes Version of the Common Terminology Criteria for Adverse Events
QTL	quality tolerance limit
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAF	Safety (analysis population)
SAP	Statistical Analysis Plan
SBI	Society of Breast Imaging
s*BRCA*mut	somatic mutation in the *BRCA* gene
SD	stable disease
SNV	single nucleotide variant
SOA	schedule of activities

Abbreviation or Specialist Term	Explanation
SOP	standard operating procedure
STEEP	Standardized Definitions for Efficacy EndPoints
t*BRCA*	tumor *BRCA*
t*BRCA*mut	tumor mutation in the *BRCA* gene
t*BRCA*wt	tumor *BRCA* wild-type
TEAE	treatment-emergent adverse event
TFST	time to first subsequent therapy
TNBC	triple-negative breast cancer
CCI [redacted]	
ULN	upper limit of normal
US	United States
WES	whole exome sequencing
WOCBP	woman of childbearing potential
WONCBP	woman of non-childbearing potential

Table 33 Glossary of terms

Term	Definition
Comparator	**Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).**
Investigational Product	**A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.**
Placebo	**An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.**
Standard of Care	**Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term.** • **Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.**

TRADEMARK INFORMATION

Trademarks of the GSK group of companies
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Trademarks not owned by the GSK group of companies
Arimidex
Aromasin
EAST
EORTC-QLQ-C30
EQ-5D-3L
FACT-GP5
Femara
FluMist
Keytruda
Lynparza
MedDRA
CCI [redacted]
PRO-CTCAE
Signatera
Soltamox

10.16. Appendix 16: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 03 02 June 2023

This amendment is considered substantial based on the criteria defined set forth in Article 10(s) of Directive 2001/20/EC of the of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Overall Rationale for the Amendment

Amendment 03 applies to all study sites. The changes are based on the Sponsor decision to permanently stop all enrollment into the ZEST[redacted]t has completed their last study procedure (as outlined in the Schedule of Activities).

List of main changes in the protocol and their rationale:

Section # and title	Description of Change	Brief Rationale
Synopsis Section 1.2 (Schema) Section 1.3 (Schedule of Activities) Section 2 (Introduction) Section 2.3.3 (Overall Benefit/Risk Conclusion) Section 4.1 (Overall Design) Section 4.4 (End of study definition) Section 5 (Study Population) – throughout, as applicable Section 6.1 (Study Treatments Administered) Section 6.3 (Measures to Minimize Bias: Randomization and Blinding) – throughout Section 6.7 (Treatment After End of Study) Section 7.1 (Withdrawal/Stopping Criteria) Section 7.2 (Participant	Updates to indicate enrollment in the study is closed and study was centrally unblinded. Participants on placebo were stopped. Requirement for specific protocol assessments and follow-up visits removed and updates to assessment (including discontinuation and/or adjusted frequency) for managing participants in Prescreening, Screening, and/or randomized in the study at the time of stopping enrollment. Participants randomized to treatment on the ZEST study may discontinue treatment and be offered scans above standard of care, while some previously specified assessments are now discontinued. Table 2 and Table 3 updated with footnotes indicating discontinued/adjusted assessments. New table summarizing participant management under Protocol Amendment 03 added (Table 11) and new schedule of assessments tables outlining expected assessments (Table 4, Table 5, Table 6). All pharmacokinetic (PK) sample collection	Due to this amendment stemming from the decision to permanently stop enrollment (outlined above), changes were made to outline the necessary assessments and management of participants in Prescreening, Screening, and/or randomized in the ZEST study at the time of implementation of the amendment, including monitoring of participants who are deriving clinical benefit from niraparib and remain on study.

Section # and title	Description of Change	Brief Rationale
Discontinuation/Withdrawal from Treatment) Section 8 (Study Assessments and Procedures) – throughout Section 10.5 (Regulatory, Ethical, and Study Oversight Considerations) Section 10.11.2 Germany (Country-specific Appendix)	is stopped. Requirement for central review of scans (BICR) removed, along with ctDNA testing requirements. Text surrounding timing of sharing genetic results relative to analyses (primary endpoint/interim) removed. End of study definition updated. At-home nursing visits will no longer be offered.	
Synopsis Section 3 (Objectives and Endpoints and Estimands) Section 8 (Study Assessments and Procedures) – throughout Section 9 (Statistical Considerations) – throughout	CCI [redacted]	
Section 5 (prescreening)	Minor updates to incorporate country-specific correction/wording.	Minor updates to consolidate country-specific agency requested changes.
Throughout	Editorial, administrative, and document formatting revisions	Minor changes for consistency, clarifications, and corrections to text, and/or necessary updates in line with current template or company style guide.

Amendment 02 FRA-1 13 Feb 2023

This amendment is considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Amendment 02 FRA-1 is a country-specific version of global Amendment 2.0 in which changes implemented in this protocol CCI [redacted]

List of main changes in the protocol and their rationale:

Section # and title	Description of Change	Brief Rationale
Throughout	Editorial, administrative, and document formatting revisions	Minor changes to align with required changes in Sponsor's updated template, style guide, and ways of working, consistency, as well as additional minor editorial changes and clarifications.
Synopsis Section 1.2 Schema Section 4.1 Overall Design Section 4.2 Scientific Rationale for Study Design Section 5 Study Population (Prescreening) Section 6.3.2 Stratification Appendix 10 Breast Cancer Staging	CCI [redacted]	
Synopsis Section 1.2 Schema (Figure 1, Figure 3) Section 1.3 Schedule of Activities (Table 2) Section 4.1 Overall Design Section 4.2 Scientific Rationale for Study Design Section 5 Study Population (Prescreening) Section 5.4 Prescreen Failures and Screen Failures	[redacted]	

Section # and title	Description of Change	Brief Rationale
	CCI [redacted]	
Synopsis Section 5 Study Population (Prescreening)	Prescreening Criterion P3 added to outline documentation of *BRCA* mutation	Updated for study conduct.
Section 2.2.5.1 Efficacy of Niraparib in Maintenance Therapy Following Platinum-based Chemotherapy Section 2.3.2 Benefit Assessment Section 4.2 Scientific Rationale for Study Design	CCI [redacted]	
Synopsis Section 5 Study Population (Prescreening)	Criterion P3 updated to P6 with addition of new criterion and text updated to clarify archival tissue requirements.	Clarification for study conduct.
Synopsis Section 1.3 Schedule of Activities (Table 3) Section 4.1 Overall Design	Screening period updated to within 6 weeks (42 days) of Day 1 and clarification this is only recommendation to start within 14 days of a confirmed positive ctDNA result.	Clarification in study conduct
Section 4.3 Justification for Dose Section 5.1 Inclusion Criteria Section 6.1.1 Niraparib (Table 12)	Mild and moderate hepatic impairment definitions updated. Gilbert's syndrome text removed from sections other than inclusion/exclusion criteria for clarification to more accurately reflect the definitions of hepatic impairment in the study for niraparib	Language alignment across sections and clarification in study conduct.
Section 5.2 Exclusion Criteria	Exclusion criterion 18 update to reflect FDA guidance. Exclusion criterion 19 corrected for typographical error.	For clarification in study conduct to align with FDA guidance and ensuring participant safety.
Section 5.1 Inclusion Criteria Appendix 4: Contraceptive and Barrier Guidance	Inclusion criterion #12 language and Appendix 4 text updated regarding male condom use and sexual intercourse	A revision of the protocol wording for use of male condoms by subjects is being made for consistency with guidance provided in the Investigator Brochure and is not a consequence of new safety information. Highly effective contraceptive methods that are user dependent updated as requested by ANSM.
Section 1.3 Schedule of Activities (Table 3) Section 6.1.1 Niraparib	Details added regarding dosing based on screening weight if there is a change in weight prior to Cycle 1/Day 1 dosing.	Clarification for study conduct
Section 1.3 Schedule of	Updated language regarding timing of	Clarification for study conduct

Section # and title	Description of Change	Brief Rationale
Activities (Table 3) Section 8.4.6 Pregnancy Testing	pregnancy tests for Screening and subsequent cycles.	
Section 6.4.1 Dose Levels and Dose Adjustment	Clarification included that dose cannot be re-escalated once reduced	Alignment with expected conduct during the study.
Section 4.1 Overall Design Section 7.1 Withdrawal/ Stopping Criteria	Updated language included regarding survival follow-up, definition of discontinuation of study intervention, and conduct of follow-up period visits.	Clarification for study conduct
Section 8.1.1 General Guidance for Treatment Continuity When Participants Are Unable to Come into the Clinic (Table 16) Appendix 11 Country-specific Requirements (Table 28)	Updated assessments to be performed by the home health services (HHS) vendor.	Clarification for study conduct to align with agreed upon assessments performed by contracted HHS vendor.
Appendix 2 Clinical Laboratory Tests Appendix 4 Contraceptive and Barrier Guidance	Updated FSH requirements for WONCBP to be <60 years	Clarification for study conduct
Synopsis Section 1.2 Schema (Figure 1) Section 4.1 Overall Design Section 5.1 Inclusion Criteria Section 8.2.1 Baseline Assessments at Screening	Inclusion criterion 1 text adjusted to clarify staging criteria. Clarifications also included throughout the protocol for the following: local t*BRCA* mutation can be somatic or germline positive, tumor staging based on clinical prognostic, pathologic prognostic, and/or anatomic staging, and Allred score included.	Clarification for study conduct
Section 1.3 Schedule of Activities (Table 3)	Note added to Table 3 indicating ECG does not need to be repeated if a patient is rescreening.	ECG is obtained for baseline documentation only and repeat is not medically indicated.
Synopsis Section 2.1 Study Rationale Section 4.1 Overall Design	Included definition for end of definitive therapy	Clarification for consistency in study conduct
Section 2.3.1 Risk Assessment (Table 6) Section 5.1 Inclusion Criteria	Inclusion criteria 8 and 9, as well as Table 6 updated to remove 3-week delay in randomization and treatment for criteria to be met.	Administrative change for clarification; text not required
Synopsis, Section 1.3 Schedule of Activities (Table 3) Section 4.1 Overall Design Appendix 3 Guidelines for Assessment of Disease, Disease Progression and Response Criteria	Imaging text update for clarification.	Clarification for study conduct.
Synopsis	Study duration updated to included overall study duration of approximately 8 years.	Editorial change for clarification regarding study conduct.
Synopsis Section 9.1 Statistical	CCI [redacted]	Clarification to align language in the protocol.

Section # and title	Description of Change	Brief Rationale
Hypotheses	CCI [redacted]	
Synopsis Section 9.4.7 Independent Data Monitoring Committee	Text updated regarding timing of safety review of Cohort 1	Clarification for study conduct
Synopsis Section 4.1 Overall Design Section 6.7 Treatment After the End of the Study	Update text surrounding potential continuation of niraparib post-end of study.	Editorial
Section 6.3.3 Blinding and Breaking the Blind	Updated text surrounding breaking the blind for those who may continue niraparib treatment at the end of the study	Clarification for study conduct
Section 8.6 Pharmacokinetics	CCI [redacted]	Clarification for study conduct
Section 9.3.2 Interim Analysis	Updated text to include HRD cutoff GIS of 42 for Cohort 2 (t*BRCA*wt/TNBC)	Clarification for study conduct.
Appendix 2 Clinical Laboratory Tests (Table 20)	Footnotes added to Table 20 to outline required laboratory tests and those to be provided if performed per standard of care.	Clarification for study conduct.
Appendix 8 AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Updates to safety reporting language	Updated to include updated template language

Amendment 02 05 Oct 2022

This amendment is considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Amendment 2.0 changes implemented in this protocol aim CCI [redacted]

List of main changes in the protocol and their rationale:

Section # and title	Description of Change	Brief Rationale
Throughout	Editorial, administrative, and document formatting revisions	Minor changes to align with required changes in Sponsor's updated template, style guide, and ways of working, consistency, as well as additional minor editorial changes and clarifications.
Synopsis Section 1.2 Schema Section 4.1 Overall Design Section 4.2 Scientific Rationale for Study Design Section 5 Study Population (Prescreening)	CCI [redacted]	

Section # and title	Description of Change	Brief Rationale
Section 6.3.2 Stratification Appendix 10 Breast Cancer Staging	CCI [redacted]	
Synopsis Section 1.2 Schema (Figure 1, Figure 3) Section 1.3 Schedule of Activities (Table 2) Section 4.1 Overall Design Section 4.2 Scientific Rationale for Study Design Section 5 Study Population (Prescreening) Section 5.4 Prescreen Failures and Screen Failures		
Synopsis Section 5 Study Population (Prescreening)		
Section 2.2.5.1 Efficacy of Niraparib in Maintenance Therapy Following Platinum-based Chemotherapy Section 2.3.2 Benefit Assessment Section 4.2 Scientific Rationale for Study Design		
Synopsis Section 5 Study Population (Prescreening)	Criterion P3 updated to P6 with addition of new criterion and text updated to clarify archival tissue requirements.	Clarification for study conduct.
Synopsis Section 1.3 Schedule of Activities (Table 3) Section 4.1 Overall Design	Screening period updated to within 6 weeks (42 days) of Day 1 and clarification this is only recommendation to start within 14 days of a confirmed positive ctDNA result.	Clarification in study conduct

Section # and title	Description of Change	Brief Rationale
Section 4.3 Justification for Dose Section 5.1 Inclusion Criteria Section 6.1.1 Niraparib (Table 12)	CCI [redacted]	
Section 5.2 Exclusion Criteria	Exclusion criterion 18 update to reflect FDA guidance. Exclusion criterion 19 corrected for typographical error.	For clarification in study conduct to align with FDA guidance and ensuring participant safety.
Section 5.1 Inclusion Criteria Appendix 4: Contraceptive and Barrier Guidance (and Appendix 11, where applicable)	Inclusion criterion #12 language and Appendix 4 text updated regarding male condom use and sexual intercourse (Appendix 11 updated, where applicable)	A revision of the protocol wording for use of male condoms by subjects is being made for consistency with guidance provided in the Investigator Brochure and is not a consequence of new safety information.
Section 1.3 Schedule of Activities (Table 3) Section 6.1.1 Niraparib	Details added regarding dosing based on screening weight if there is a change in weight prior to Cycle 1/Day 1 dosing.	Clarification for study conduct
Section 1.3 Schedule of Activities (Table 3) Section 8.4.6 Pregnancy Testing	Updated language regarding timing of pregnancy tests for Screening and subsequent cycles.	Clarification for study conduct
Section 6.4.1 Dose Levels and Dose Adjustment	Clarification included that dose cannot be re-escalated once reduced	Alignment with expected conduct during the study.
Section 4.1 Overall Design Section 7.1 Withdrawal/ Stopping Criteria	Updated language included regarding survival follow-up, definition of discontinuation of study intervention, and conduct of follow-up period visits.	Clarification for study conduct
Section 8.1.1 General Guidance for Treatment Continuity When Participants Are Unable to Come into the Clinic (Table 16) Appendix 11 Country-specific Requirements (Table 28)	Updated assessments to be performed by the home health services (HHS) vendor.	Clarification for study conduct to align with agreed upon assessments performed by contracted HHS vendor.
Appendix 2 Clinical Laboratory Tests Appendix 4 Contraceptive and Barrier Guidance	Updated FSH requirements for WONCBP to be <60 years	Clarification for study conduct
Synopsis Section 1.2 Schema (Figure 1) Section 4.1 Overall Design Section 5.1 Inclusion Criteria Section 8.2.1 Baseline Assessments at Screening	Inclusion criterion 1 text adjusted to clarify CCI [redacted]	Clarification for study conduct
Section 1.3 Schedule of Activities (Table 3)	Note added to Table 3 indicating ECG does not need to be repeated if a patient is rescreening.	ECG is obtained for baseline documentation only and repeat is not medically indicated.

Section # and title	Description of Change	Brief Rationale
Synopsis Section 2.1 Study Rationale Section 4.1 Overall Design	Included definition for end of definitive therapy	Clarification for consistency in study conduct
Section 2.3.1 Risk Assessment (Table 6) Section 5.1 Inclusion Criteria	Inclusion criteria 8 and 9, as well as Table 6 updated to remove 3-week delay in randomization and treatment for criteria to be met.	Administrative change for clarification; text not required
Synopsis, Section 1.3 Schedule of Activities (Table 3) Section 4.1 Overall Design Appendix 3 Guidelines for Assessment of Disease, Disease Progression and Response Criteria	Imaging text update for clarification.	Clarification for study conduct.
Synopsis	Study duration updated to included overall study duration of approximately 8 years.	Editorial change for clarification regarding study conduct.
Synopsis Section 9.1 Statistical Hypotheses	CCI [redacted]	Clarification to align language in the protocol.
Synopsis Section 9.4.7 Independent Data Monitoring Committee	Text updated regarding timing of safety review of Cohort 1	Clarification for study conduct
Synopsis Section 4.1 Overall Design Section 6.7 Treatment After the End of the Study	Update text surrounding potential continuation of niraparib post-end of study.	Editorial
Section 6.3.3 Blinding and Breaking the Blind	Updated text surrounding breaking the blind for those who may continue niraparib treatment at the end of the study	Clarification for study conduct
Section 8.6 Pharmacokinetics	Updated to include sample collection for liver events.	Clarification for study conduct
Section 9.3.2 Interim Analysis	CCI [redacted]	Clarification for study conduct.
Appendix 2 Clinical Laboratory Tests (Table 20)	Footnotes added to Table 20 to outline required laboratory tests and those to be provided if performed per standard of care.	Clarification for study conduct.
Appendix 8 AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Updates to safety reporting language	Updated to include updated template language
Appendix 11 Country-specific Requirements	New appendix outlining country-specific requirements	New appendix per protocol template outlining country-specific difference previously outlined in country-specific amendments.

Amendment 01: 22 Feb 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Amendment 01 FRA is a country-specific version of global Amendment 01, CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
Headers, cover page, Synopsis, Section 3, Section 5.4, Section 7, Section 8.5.6, Section 8.7, Appendix 2, Appendix 5, Appendix 8 AEs and SAEs, Appendix 10 Protocol Amendment Summary of Changes, Section 11, and throughout the document.	Headers and cover page were updated with new version number. Protocol Amendment Summary of Changes section was added to include rationale for this amendment. Formatting adjustments made throughout. References added, as needed, to support changes.	Editorial changes and formatting updates to align with the Sponsor's updated standard protocol template and ways of working, including description of estimands described in the SAP.
Section 1.1 Synopsis Section 1.3 Schedule of Activities, Table 3 Section 4.1 Overall Study Design Section 5.1 Inclusion Criteria (criteria #11 and #12) Section 5.2 Exclusion Criteria (criterion #17) Section 8.4.6 Pregnancy Testing Section 8.5.5 Pregnancy Appendix 4 Contraceptive and Barrier Guidance, Table 20	CCI [redacted]	
Synopsis Section 5 Study Population Section 5.1 Inclusion Criteria (Criterion #1)		

Section # and Name	Description of Change	Brief Rationale
	CCI [redacted]	
Synopsis Section 1.2, Figure 2 (Study Schema) Section 1.3, Table 2 (Prescreening) Section 5 Study Population Section 5.1 Inclusion Criteria (criterion #2)		

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schema, Figure 1 Section 1.3 Schedule of Activities, Table 2 (Prescreening) Section 4.1 Overall Design (ctDNA prescreening)	CCI [redacted]	[redacted]
Section 1.3 Schedule of Activities, Table 3 Section 6.4.1 Dose Levels and Dose Adjustments Section 6.8 Concomitant Medications and Nondrug Therapies Section 6.8.1 Prohibited Medication and Drug Therapies	Concomitant medications clarified to reference eCRF completion guidelines regarding collection of additional therapies (endocrine therapy, ovarian suppression, bisphosphonates/denosumab, and pembrolizumab). Updated to indicate concurrent pembrolizumab use is permitted and remove immunotherapies. Guidance provided that for participants on concurrent that endocrine or pembrolizumab decisions regarding dose interruptions/modifications should be made independently.	Clarification for study conduct surrounding permitted therapies and collection of concomitant medications including endocrine therapy, ovarian suppression, bisphosphonates/denosumab, and pembrolizumab use. The Sponsor has provided clarifying language in the protocol to allow Investigators flexibility with needed dose adjustments for those breast cancer treatment medications not directly administered by the protocol, i.e., endocrine therapies and pembrolizumab.
Section 5.1 Inclusion Criteria (criterion #5)	Updated to remove details of specimen handling and only refer to Study Reference Manual and added clarification that	Clarification for inclusion criteria. While adequate quality and quantity of tumor tissue remains an important eligibility requirement for study

Section # and Name	Description of Change	Brief Rationale
	archival tissue refers to prescreening archival tissue.	enrolment, the Sponsor has been able to provide increased flexibility for tissue requirements, and anticipate further improvements to technology over the course of the study. Therefore, specific parameters have been removed from the protocol in the best interest of the participants.
Section 5.1 Inclusion Criteria (criterion #8)	Creatinine clearance added to eligibility criteria instead of serum creatinine, as well as clarification notes regarding adequate renal function, hepatic impairment, and creatinine clearance.	Creatinine clearance was changed to align with other niraparib studies. An upper limit of ALT was added for participant safety.
Section 5.2 Exclusion Criteria (criterion #9) Section 6.8 Concomitant Medications and Nondrug Therapies Section 6.8.1 Prohibited Medications and Nondrug Therapies Appendix 3 Guidelines for Assessment of Disease, Disease Progression and Response Criteria	Updated language surrounding COVID-19 vaccine, recommendations, timing, and information to be entered in the eCRF. Guidance regarding thrombocytopenia associated with mRNA vaccines included. Guidance included surrounding lymphadenopathy after COVID-19 vaccinations and tumor assessments.	Updated based on Sponsor guidance regarding the COVID-19 vaccines reflecting current evolving medical practice, tumor assessments, and for study conduct to record the data, as effects of concomitant COVID-19 vaccine used with niraparib are not known.
Section 5.2 Exclusion Criteria (criterion #19)	Exclusion criterion updated allowing immunocompromised participants.	Amended criteria to allow immunocompromised participants with HIV. Based on accumulated safety data for niraparib and immunocompromised participants, and precedent set by other niraparib studies. Patients with well-controlled HIV may be eligible for enrollment onto the ZEST study.
Section 1.3 Schedule of Activities Table 3 Section 8.4.3 Vital signs	Updated notes and text to clarify that 3 readings for blood pressure measurements are only recommendations and vital signs may be taken at a local laboratory/clinic or at-home nursing visits for specific visits.	Clarification for study conduct that 3 blood pressure readings are not required. As per clinical standard-of-care, a single blood pressure measurement is sufficient for safety monitoring. Because it is important for participant safety to ensure that blood pressure is recorded weekly for the first 8 weeks, the Sponsor has provided flexibility in terms of options for where the participant may complete these assessments.
Section 1.3 Schedule of Activities, Table 4 (PK Sampling for All Participants) Section 1.3 Schedule of Activities, Table 5 (PK Sampling for PK Substudy) Section 8.6 Pharmacokinetics	Updated notes/text to indicate participants must switch to morning niraparib dosing 1 week prior to PK testing. Updated footnotes/text regarding blood samples to include the transition of morning dosing 1 week prior to PK	Clarification in study conduct. PK analysis is an important aspect of the ZEST study. As such, the timing of niraparib and endocrine therapy dosing should align with the timing of planned PK sampling. Clarifying language has been added to the protocol to ensure that the samples drawn for PK analysis can be

Section # and Name	Description of Change	Brief Rationale
	testing for niraparib and 2 weeks prior to PK testing for endocrine therapy at Cycle 1/Day 15.	accurately interpreted to ensure the safety of the participants.
Section 8.8 Translational Research Appendix 5 Regulatory, Ethical, and Study Oversight Considerations	Included text regarding incidental tumor mutation findings released to the Investigator and timing.	CCI [redacted]
Appendix 2 Clinical Laboratory Tests, Table 18	List of laboratory parameters updated including addition of total and direct bilirubin, and removal of amylase, magnesium, phosphorus, and uric acid from clinical chemistry parameters. Urinalysis parameter removed and text updated.	Clarification for study conduct as amylase is not necessary for monitoring pancreatitis during niraparib treatment. Bilirubin specification added for liver toxicity monitoring. Unnecessary laboratory assessments removed, and clarification in study conduct pertaining to urinalysis to accommodate local standard of care. Bilirubin had been erroneously omitted from the Table, and so, has been added for participant safety. Other deleted laboratory parameters were those deemed unnecessary for safety monitoring of participants and were therefore, removed or modified. Amylase, magnesium, phosphorus, and uric acid are not typically included in standard-of-care clinical chemistry panels and niraparib has not been shown to specifically cause abnormalities in these parameters. Similarly, specific urinalysis parameters were removed to allow local standard-of-care evaluation for the presence of baseline urinary infection.
Appendix 4, Contraceptive and Barrier Guidance, Table 21	Updated to specify only nonhormonal IUDs permitted. Added barrier methods of contraception.	Clarification for study conduct and to include acceptable user-dependent, highly effective contraceptive options to be consistent with current standard of care in breast oncology clinical practice. This change supports patient safety and is an important additional option for participants.

Section # and Name	Description of Change	Brief Rationale
Appendix 6 Liver Safety Require Actions and Follow-up Assessments, Table 22	Added clarification surrounding HPLC for serum acetaminophen is only required as per local standard of care.	Clarification in study conduct to accommodate local standard of care. While this laboratory assessment may be helpful in determining the cause of liver injury, it is not strictly essential in the evaluation and may not be available in all study locations.
Synopsis Section 1.3 Schedule of Activities Table 3 Section 3 Objectives and Endpoints Section 4.1 Overall design Section 8.2.2 Baseline CT/MRI and Bone Scan Section 8.3.1 Postbaseline Imaging and Tumor Assessment Section 8.3.11 Exploratory Efficacy Endpoint (Time to Brain Progression) Section 9.4.3 Exploratory Efficacy Analyses Appendix 3 Guidelines for Assessment of Disease, Disease Progression and Response Criteria - adapted from RECIST v1.1	Addition of new exploratory endpoint regarding time to brain progression including clarification that IV contrast-enhanced MRI is preferred for brain imaging if brain metastasis suspected.	New exploratory endpoint exploring brain metastasis and clarification for study conduct as IV contrast is more sensitive for detection of brain metastasis.
Synopsis, Objectives and Endpoints Section 3 Objectives and Endpoints Section 8.3.2 Primary Efficacy Endpoint, Table 15 Definitions o Efficacy Endpoints Section 8.3.10 Exploratory Efficacy Endpoint (IBCFS) Section 9.4.3 Exploratory Efficacy Analyses	[redacted]	[redacted]
Synopsis, Objectives and Endpoints Section 3 Objectives and Endpoints Section 8.3.9 Exploratory Efficacy Endpoint (IDFS)		
Synopsis, Objectives and Endpoints Section 3 Objectives and Endpoints	Adjusted wording of safety endpoints and removed physical examinations and analyses will be conducted as outlined in the SAP.	Clarification for analysis; physical examination data are not collected on eCRFs for analysis. This clarification regarding the physical exam was to ensure alignment with the eCRF.
Synopsis Section 1.3 Schedule of Activities, Table 2 Prescreening, Section 4,1 Overall Design Section 5.1 Inclusion Criteria	Updated start of endocrine therapy for eligible participants to 3 months prior to randomization.	Editorial change. Protocol clarification; “prior to enrollment” is unclear. Original intent was 3 months prior to starting niraparib.

Section # and Name	Description of Change	Brief Rationale
(criterion #3)		
Synopsis Section 1.2 Schema, Figure 1 Section 1.3 Schedule of Activities, Table 3 Section 4.1 Overall Design Section 8.2.1 Baseline Assessments at Screening	Updated text regarding start of Screening Period with respect to confirmation of detectable ctDNA and quality of prescreening tissue samples.	Editorial change to clarify start of Screening period for study conduct.
Synopsis Section 1.2 Schema, Figure 2 Section 4.1 Overall Design Section 6.3.2 Stratification	Added text, as well as a footnote to Figure 2 to indicate time of last intervention is defined as the date of most recent oncological surgery, date of last adjuvant chemotherapy, or date of last radiotherapy fraction, whichever occurred later.	Editorial change to clarify time of last intervention.
Synopsis	Clarified that main ICF should be signed before screening starts.	Clarification statement to comply with GCP.
Synopsis Section 5 Study Population Section 5.4 Prescreen Failures and Screen Failures	Prescreening criteria numbered and incorporated prescreen failures along with screen failures in renamed section.	Formatting change to align Prescreening criteria with eCRFs
Section 5.1 Inclusion Criteria	Specified that participants must meet prescreening criteria to be included in the study	Editorial change for clarification regarding participants' inclusion in the study.
Synopsis Section 1.2 Schema Section 5 Study Population Prescreening (criterion #P2)	Added text indicating prescreening should be started as soon as possible, prior to completion of adjuvant therapy.	Editorial changes for clarification in study conduct.
Section 5.2 Exclusion Criteria (criterion #2)	Added text regarding ovarian suppression treatment as a permitted medication.	Editorial change for consistency with rest of protocol.
Synopsis Section 5.2 Exclusion Criteria (criterion #4) Appendix 1 Exclusion of Participants Who Have Shown No Definitive Response to Preoperative Chemotherapy	Clinical evaluation added as criteria for evaluation of no definitive response and additional information added for evaluation of no definitive response criteria	Clarification for study conduct. Text updated to clarify methods for assessment of no definitive response with no impact on participant safety, study conduct, or study interpretation.
Section 1.2 Study Schema, Figure 2	Key eligibility criteria updated	Administrative change to align with protocol text.
Section 1.2 Schema, Figure 1 Section 1.3 Schedule of Activities, Table 2 Prescreening Section 4.1 Overall Design	Changed "final cycle" for initiation of prescreening platform to "last 6 weeks of chemotherapy and radiation adjuvant treatment" in notes/footnotes.	Editorial change to provide clarification with a measurable time definition for specific adjuvant treatment.
Section 1.3 Schedule of Activities Table 2 (Prescreening) Section 1.3 Schedule of Activities, Table 3	Included note regarding regimen stability for HR+ participants in Cohort 1 on endocrine therapy. Updated note for pathology report to indicate it will accompany samples sent for testing.	Formatting/editorial clarification for study conduct to align with protocol text and intended data collection for screening versus prescreening periods, and analysis. There is no change to the information collected as part of the clinical study; this change only represents a clarification of

Section # and Name	Description of Change	Brief Rationale
	Assessments added to Prescreening activities (eligibility; demography; disease characteristics; anticancer, radiation therapies; surgical procedures for current indication prior to Screening; and AEs). Similarly, activities related to Demography, disease characteristics, and tumor characteristics removed from Table 3, anticancer therapies updated to clarify only prior anticancer therapies for historical cancers, and notes updated. Medical history notes updated to outline information to be captured.	when the data are collected, i.e., no impact on safety and no significant impact on study conduct, or study interpretation.
Section 1.3 Schedule of Activities, Table 3 Section 8.4.6 Pregnancy Testing Appendix 2 Clinical Laboratory Tests, Table 18 Appendix 4 Contraceptive and Barrier Guidance	Notes and text requiring serum pregnancy testing adjusted and footnote removed in Table 18 (previously Table 17).	Clarification for consistency in study conduct regarding pregnancy testing requirements.
Section 1.3 Schedule of Activities, Table 3 Section 8.8.1 Tumor Tissue Collection at Time of Disease Recurrence	Added footnote and text indicating optional biopsies must be performed before initiating new anticancer therapy and do not need to occur within 7-days of last dose.	Editorial change to provide clarification for study conduct.
Section 1.3 Schedule of Activities, Table 3 Section 8.9 Patient Reported Outcome Measures Section 8.9.5 Patient Global Impression Items	Updated note for PRO collection to be completed on the assigned clinic visit day and for PGIC to indicate it will be collected starting on Cycle 2/Day 1 and every 28 days thereafter.	Editorial change to provide clarification for study conduct.
Section 1.3 Schedule of Activities Table 2 (Disease Characteristics) Table 3 (Eligibility)	Included note regarding recurrence during prescreening/screening and information to be collected.	Editorial change to provide clarification for study conduct.
Section 1.3 Schedule of Activities Table 3	Updated notes to specify difference in visit windows for monthly versus weekly visits.	Editorial clarification for study conduct.
Section 1.3 Schedule of Activities Table 3 Section 8.3.1 Postbaseline Imaging and Tumor Assessment	Text regarding CT or MRI for DFS updated to include: (Year 1 Weeks 12, 24, 36, 48; Year 2, Weeks 60, 72, 84, 96) and notes updated regarding PET scan, and that imaging should continue within the defined interval windows.	Editorial clarification for the Investigator.
Section 1.3 Schedule of Activities Table 3	Note added to anticancer therapy following study	Administrative change for omission in the original protocol for the evaluation of the

Section # and Name	Description of Change	Brief Rationale
	treatment indicating any new anticancer treatment started before the Safety Follow-up Visit must be collected during this visit as outlined in eCRF completion instructions.	safety of niraparib in this population.
Section 1.3 Schedule of Activities, Table 3	Hematology and clinical chemistry blood draw visit windows for specific visits	Editorial clarification for study conduct providing flexibility in blood draws.
Section 1.3 Schedule of Activities, Table 3	CCI [redacted]	Editorial change to align with protocol text.
Section 1.3 Schedule of Activities, Table 3 (Niraparib or placebo dispensed/collected)	Note added regarding recording missed doses.	Editorial change to align with data collection in eCRFs.
Section 1.3 Schedule of Activities, Table 4 PK Sampling Schedule for All Participants	Removed text regarding holding dose 1 day prior to Cycle 2/Day 1	Administrative change to correct error in original protocol.
Synopsis Section 4.1 Overall design Section 4.2 Overall Rationale for Study Design Sections 8.8 Translational Research Section 9.3.2 Interim Analysis	Included name of assay for tumor *BRCA*/HRD testing.	Administrative change for clarification for study conduct and for regulatory/ethics approval of the assay as part of the current protocol and any necessary reporting requirements related to assay use in this study.
Section 6.8 Concomitant Medications and Nondrug Therapies	Concomitant medication follow-up corrected to indicate that it continues until the Safety follow-up visit after end of treatment and not until end of study.	Administrative change to provide clarification for study conduct.
Section 4.1 Overall Design Section 8.1.1 General Guidance for Treatment Continuity When Participants Are Unable to Come into the Clinic, Table 14 Section 8.6 Pharmacokinetics	Updated to include at-home nursing services (or local laboratory/clinic) and clarification of study days for these visits if participants are unable to attend clinic visits.	Administrative change to provide clarification for participants' safety during the COVID-19 pandemic.
Section 1.3 Schedule of Activities, Table 2 Prescreening Section 8.8 Translational Research	Adjusted protocol text to refer to Study Reference Manual for details.	Editorial change to provide clarification of tissue requirements per vendor performing the analysis outlined in the study reference manual.
Section 2.2.2 Treatment Options for Patients with Operable HER2− Breast Cancer Section 2.2.4 PARP Inhibitors Section 2.2.5.2 Efficacy of Niraparib in Breast Cancer (Study 3000-PN162-01-001 TOPACIO) Section 2.2.5.4 Niraparib and Pembrolizumab Section 2.2.6 Circulating Tumor DNA	CCI [redacted]	

Section # and Name	Description of Change	Brief Rationale
Section 2.3.2 Benefit Assessment Section 2.3.3 Overall Benefit/Risk Conclusion Section 4.2 Scientific Rationale for Study Design	CCI [redacted]	
Section 4.3 Justification for Dose	Amended language for niraparib dosing in participants with moderate hepatic impairment.	Administrative change to align with the IB.
Section 6 Study Treatments and Concomitant Therapy	Updated references to Pharmacy Manual to Study Reference Manual	Administrative change to correction text throughout protocol as study does not have a Pharmacy Manual.
Section 6.1.1 Niraparib	Text corrected regarding [CCI redacted] provided for dosing with up to 3 days flexibility.	Administrative change to correction text and align with Table 3 visit window.
Section 6.1.1 Niraparib, Table 10	Updated footnotes regarding hepatic impairment definitions.	Editorial change to provide clarification for participant safety.
Section 6.1.1 Niraparib	Included text that dose escalation not permitted once initial starting dose is assigned.	Editorial change for clarification of study conduct.
Section 6.3.1 Randomization	Removed IVRS and reference to phone numbers.	Editorial change to correction align protocol text regarding randomization procedures being used in the study.
Section 6.3.3 Blinding and Breaking the Blind	Deleted text regarding unblinded third party not relevant to the study.	Editorial change to correct text to align with study.
Synopsis Section 4.1 Overall Design Section 7.1 Withdrawal/Stopping Criteria	Updated text regarding duration of treatment.	Editorial clarification for study conduct.
Section 7.1 Withdrawal/Stopping Criteria	Updated text regarding withdrawal of participants with additional primary malignancies other than MDS and AML and regarding possibility of continued niraparib treatment if participants are discontinued.	Editorial change for clarification
Synopsis Section 7.3.1 Further Biomedical Research Maintaining Confidential Participant Information	Clarification that Further Biomedical Research is after study completion.	Administrative change to align with ICF text.
Synopsis Section 8.8 Translational Research Appendix 9 Use/Analysis of DNA	Clarification regarding possible use of tumor tissue and blood samples for exploratory research. Appendix heading updated and clarified DNA samples can be	Editorial changes for clarification

Section # and Name	Description of Change	Brief Rationale
	derived from tumor or blood specimens.	
Section 8.1.1 General Guidance for Treatment Continuity When Participants Are Unable to Come into the Clinic Section 8.1.1, Table 14	Removed text pertaining to global telemedicine and updated Table 14 (previously Table 13) table title for clarification.	Editorial changes for Clarification that Sponsor not providing global telemedicine services; sites to engage their own local platform.
Section 8.1.1.1 Direct to Participant Investigational Medicinal Product Shipments	Revised text to remove drug supply vendor name.	Administrative correction.
Section 8.5 Adverse Events, Serious Adverse Events, and Other Safety Reporting Appendix 5 Regulatory, Ethical, and Study Oversight Considerations	Removed mention of LAR.	Administrative change to align with inclusion criterion 13.
Section 8.5.6 Cardiovascular and Death Events	Clarification regarding the recording of death information in eCRFs.	Administrative change to provide clarification for collection of death information aligned with eCRFs.
Section 8.7 Genetics	Updated section heading and language regarding WES testing.	Administrative change to provide clarification in protocol text.
Section 9.4.5.1 Pharmacokinetic Parameters	Clarifications in PK language and GSK analysts access to PK datasets.	Administrative change to align with PK and Exposure-Response Analysis Plan as per regulatory agency recommendation and for clarification on access to data.
Appendix 3 Guidelines for Assessment of Disease, Disease Progression and Response Criteria	Updated criteria for participants with no evidence of disease at baseline.	Editorial changes to provide clarification for study conduct.

Amendment DEU-4: 07 January 2022

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

Amendment DEU-4 is a country-specific protocol amendment of country-specific Amendment 01/DEU-3, CCI [redacted].

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1 General Guidance for Treatment Continuity When Participants Are Unable to Come into the Clinic	'Limited physical examination including symptom-directed physical examinations' has been removed from the list of functions home nursing services may perform.	German specific requirements have been applied, as physical examinations can only be performed by a physician, implemented at the request of BfArM.
Section 10.4, Appendix 4: Contraceptive and Barrier	The following text has been removed from the "Highly Effective Methods	German specific requirements have been applied with regards to

Section # and Name	Description of Change	Brief Rationale
Guidance	that Are User Dependent" section of Table 21: • Barrier methods of contraception - Acceptable barrier methods of contraception include the following: male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods). The use of double-barrier methods should always be supplemented with the use of a spermicide to result in a failure rate of <1%. Female condom and male condom should not be used together.	contraceptives allowed during the study, implemented at the request of BfArM.

Amendment 01/DEU-3: 07 October 2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Amendment 01 is a global protocol amendment [redacted]

Section # and Name	Description of Change	Brief Rationale
Headers, cover page, Synopsis, Section 3, Section 5.4, Section 7, Section 8.5.6, Section 8.7, Appendix 2, Appendix 5, Appendix 8 AEs and SAEs, Appendix 10 Protocol Amendment Summary of Changes, Section 11, and throughout the document.	Headers and cover page were updated with new version number. Protocol Amendment Summary of Changes section was added to include rationale for this amendment. Formatting adjustments made throughout. References added, as needed, to support changes.	Editorial changes and formatting updates to align with the Sponsor's updated standard protocol template and ways of working, including description of estimands described in the SAP.
Synopsis Section 5 Study Population Section 5.1 Inclusion Criteria (Criterion #1)	Added definition for TNBC (ER and progesterone receptor <1% and HER2 negative by FISH or IHC staining 0 or 1+). Included details to clarify eligibility for participants with multifocal tumors and clarify that multicentric and bilateral breast cancers are not allowed.	Important clarification for participant eligibility. This revision was made to the protocol to specifically define the parameters for TNBC, as definitions can vary across countries and local practices. Because assignment to a TNBC status versus a HR+ status can have significant implications for treatment selection, it was important for study conduct to clarify the eligible TNBC population for the ZEST study. In addition, the sponsor needed to clarify the acceptability of multifocal tumors with similar histology but exclusion of multicentric and bilateral

Section # and Name	Description of Change	Brief Rationale
		breast cancers to ensure ctDNA results are reflective of a single breast cancer entity. This is to ensure accurate interpretation of the study endpoints because the bespoke ctDNA platform may vary across different tumors. Multifocal disease is usually defined as involvement of several areas within a breast quadrant, which typically represents a single disease entity occurring along an entire duct. In contrast, multicentric disease involves multiple areas within different quadrants, typically representing involvement of multiple ducts with potentially distinct index tumors.
Synopsis Section 1.2, Figure 2 (Study Schema) Section 1.3, Table 2 (Prescreening) Section 5 Study Population Section 5.1 Inclusion Criteria (criterion #2)	Added regarding participants with HR+HER2− t*BRCA*mut breast cancer may be receiving concurrent adjuvant endocrine therapy, all participants may be receiving concurrent adjuvant bisphosphonates or adjuvant pembrolizumab, if clinically indicated. Figure footnote updated to indicate concurrent adjuvant pembrolizumab is permitted.	Clarification that endocrine, bisphosphonates or denosumab, and pembrolizumab therapies are allowed. CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
	CCI [redacted]	
Section 1.2 Schema, Figure 1 Section 1.3 Schedule of Activities, Table 2 (Prescreening) Section 4.1 Overall Design (ctDNA prescreening)		
Section 1.3 Schedule of Activities, Table 3 Section 6.4.1 Dose Levels and Dose Adjustments Section 6.8 Concomitant Medications and Nondrug Therapies Section 6.8.1 Prohibited Medication and Drug Therapies	Concomitant medications clarified to reference eCRF completion guidelines regarding collection of additional therapies (endocrine therapy, ovarian suppression, bisphosphonates/denosumab, and pembrolizumab). Updated to indicate concurrent pembrolizumab use is permitted and remove immunotherapies. Guidance provided that for participants on concurrent that endocrine or pembrolizumab decisions regarding dose interruptions/modifications should be made independently.	Clarification for study conduct surrounding permitted therapies and collection of concomitant medications including endocrine therapy, ovarian suppression, bisphosphonates/denosumab, and pembrolizumab use. The Sponsor has provided clarifying language in the protocol to allow Investigators flexibility with needed dose adjustments for those breast cancer treatment medications not directly administered by the protocol, i.e., endocrine therapies and pembrolizumab.
Section 5.1 Inclusion Criteria (criterion #5)	Updated to remove details of specimen handling and only refer to Study Reference Manual	Clarification for inclusion criteria. While adequate quality and quantity of tumor tissue remains an important

Section # and Name	Description of Change	Brief Rationale
	and added clarification that archival tissue refers to prescreening archival tissue.	eligibility requirement for study enrolment, the Sponsor has been able to provide increased flexibility for tissue requirements, and anticipate further improvements to technology over the course of the study. Therefore, specific parameters have been removed from the protocol in the best interest of the participants.
Section 5.1 Inclusion Criteria (criterion #8)	Creatinine clearance added to eligibility criteria instead of serum creatinine, as well as clarification notes regarding adequate renal function, hepatic impairment, and creatinine clearance.	Creatinine clearance was changed to align with other niraparib studies. An upper limit of ALT was added for participant safety.
Section 5.1 Inclusion Criteria (criterion #12) Appendix 4 Contraceptive and Barrier Guidance, Table 20	Recommendations for duration of contraception use for male participants was updated to continue for 90 days, rather than 180 days, after the last dose of study treatment.	Clarification for participant safety in alignment with the current IB.
Section 5.2 Exclusion Criteria (criterion #9) Section 6.8 Concomitant Medications and Nondrug Therapies Section 6.8.1 Prohibited Medications and Nondrug Therapies Appendix 3 Guidelines for Assessment of Disease, Disease Progression and Response Criteria	Updated language surrounding COVID-19 vaccine, recommendations, timing, and information to be entered in the eCRF. Guidance regarding thrombocytopenia associated with mRNA vaccines included. Guidance included surrounding lymphadenopathy after COVID-19 vaccinations and tumor assessments.	Updated based on Sponsor guidance regarding the COVID-19 vaccines reflecting current evolving medical practice, tumor assessments, and for study conduct to record the data, as effects of concomitant COVID-19 vaccine used with niraparib are not known.
Section 5.2 Exclusion Criteria (criterion #19)	Exclusion criterion updated allowing immunocompromised participants.	Amended criteria to allow immunocompromised participants with HIV. Based on accumulated safety data for niraparib and immunocompromised participants, and precedent set by other niraparib studies. Patients with well-controlled HIV may be eligible for enrollment onto the ZEST study.
Section 1.3 Schedule of Activities Table 3 Section 8.4.3 Vital signs	Updated notes and text to clarify that 3 readings for blood pressure measurements are only recommendations and vital signs may be taken at a local laboratory/clinic or at-home nursing visits for specific visits.	Clarification for study conduct that 3 blood pressure readings are not required. As per clinical standard-of-care, a single blood pressure measurement is sufficient for safety monitoring. Because it is important for participant safety to ensure that blood pressure is recorded weekly for the first 8 weeks, the Sponsor has provided flexibility in terms of options for where the participant may complete these assessments.
Section 1.3 Schedule of	Updated notes/text to indicate	Clarification in study conduct.

Section # and Name	Description of Change	Brief Rationale
Activities, Table 4 (PK Sampling for All Participants) Section 1.3 Schedule of Activities, Table 5 (PK Sampling for PK Substudy) Section 8.6 Pharmacokinetics	participants must switch to morning niraparib dosing 1 week prior to PK testing. Updated footnotes/text regarding blood samples to include the transition of morning dosing 1 week prior to PK testing for niraparib and 2 weeks prior to PK testing for endocrine therapy at Cycle 1/Day 15.	PK analysis is an important aspect of the ZEST study. As such, the timing of niraparib and endocrine therapy dosing should align with the timing of planned PK sampling. Clarifying language has been added to the protocol to ensure that the samples drawn for PK analysis can be accurately interpreted to ensure the safety of the participants.
Section 8.8 Translational Research Appendix 5 Regulatory, Ethical, and Study Oversight Considerations	Included text regarding incidental tumor mutation findings released to the Investigator and timing.	Clarification for study conduct. CCI [redacted]
Appendix 2 Clinical Laboratory Tests, Table 18	List of laboratory parameters updated including addition of total and direct bilirubin, and removal of amylase, magnesium, phosphorus, and uric acid from clinical chemistry parameters. Urinalysis parameter removed and text updated.	Clarification for study conduct as amylase is not necessary for monitoring pancreatitis during niraparib treatment. Bilirubin specification added for liver toxicity monitoring. Unnecessary laboratory assessments removed, and clarification in study conduct pertaining to urinalysis to accommodate local standard of care. Bilirubin had been erroneously omitted from the Table, and so, has been added for participant safety. Other deleted laboratory parameters were those deemed unnecessary for safety monitoring of participants and were therefore, removed or modified. Amylase, magnesium, phosphorus, and uric acid are not typically included in standard-of-care clinical chemistry panels and niraparib has not been shown to specifically cause abnormalities in these parameters. Similarly, specific urinalysis parameters were removed to allow local standard-of-care evaluation for the presence of baseline urinary infection.
Appendix 4, Contraceptive and Barrier Guidance, Table 21	Updated to specify only nonhormonal IUDs permitted. Added barrier methods of	Clarification for study conduct and to include acceptable user-dependent, highly effective contraceptive options to be

Section # and Name	Description of Change	Brief Rationale
	contraception.	consistent with current standard of care in breast oncology clinical practice. This change supports patient safety and is an important additional option for participants.
Appendix 6 Liver Safety Require Actions and Follow-up Assessments, Table 22	Added clarification surrounding HPLC for serum acetaminophen is only required as per local standard of care.	Clarification in study conduct to accommodate local standard of care. While this laboratory assessment may be helpful in determining the cause of liver injury, it is not strictly essential in the evaluation and may not be available in all study locations.
Synopsis Section 1.3 Schedule of Activities Table 3 Section 3 Objectives and Endpoints Section 4.1 Overall design Section 8.2.2 Baseline CT/MRI and Bone Scan Section 8.3.1 Postbaseline Imaging and Tumor Assessment Section 8.3.11 Exploratory Efficacy Endpoint (Time to Brain Progression) Section 9.4.3 Exploratory Efficacy Analyses Appendix 3 Guidelines for Assessment of Disease, Disease Progression and Response Criteria - adapted from RECIST v1.1	Addition of new exploratory endpoint regarding time to brain progression including clarification that IV contrast-enhanced MRI is preferred for brain imaging if brain metastasis suspected.	New exploratory endpoint exploring brain metastasis and clarification for study conduct as IV contrast is more sensitive for detection of brain metastasis.
Synopsis, Objectives and Endpoints Section 3 Objectives and Endpoints Section 8.3.2 Primary Efficacy Endpoint, Table 15 Definitions of Efficacy Endpoints Section 8.3.10 Exploratory Efficacy Endpoint (IBCFS) Section 9.4.3 Exploratory Efficacy Analyses	CCI	CCI
Synopsis, Objectives and Endpoints Section 3 Objectives and Endpoints Section 8.3.9 Exploratory Efficacy Endpoint (IDFS)		
Synopsis, Objectives and Endpoints Section 3 Objectives and Endpoints	Adjusted wording of safety endpoints and removed physical examinations and analyses will be conducted as outlined in the SAP.	Clarification for analysis; physical examination data are not collected on eCRFs for analysis. This clarification regarding the physical exam was to ensure alignment with the eCRF.

Section # and Name	Description of Change	Brief Rationale
Synopsis Section 1.3 Schedule of Activities, Table 2 Prescreening, Section 4,1 Overall Design Section 5.1 Inclusion Criteria (criterion #3)	Updated start of endocrine therapy for eligible participants to 3 months prior to randomization.	Editorial change. Protocol clarification; “prior to enrollment” is unclear. Original intent was 3 months prior to starting niraparib.
Synopsis Section 1.2 Schema, Figure 1 Section 1.3 Schedule of Activities, Table 3 Section 4.1 Overall Design Section 8.2.1 Baseline Assessments at Screening	Updated text regarding start of Screening Period with respect to confirmation of detectable ctDNA and quality of prescreening tissue samples.	Editorial change to clarify start of Screening period for study conduct.
Synopsis Section 1.2 Schema, Figure 2 Section 4.1 Overall Design Section 6.3.2 Stratification	Added text, as well as a footnote to Figure 2 to indicate time of last intervention is defined as the date of most recent oncological surgery, date of last adjuvant chemotherapy, or date of last radiotherapy fraction, whichever occurred later.	Editorial change to clarify time of last intervention.
Synopsis	Clarified that main ICF should be signed before screening starts.	Clarification statement to comply with GCP.
Synopsis Section 5 Study Population Section 5.4 Prescreen Failures and Screen Failures	Prescreening criteria numbered and incorporated prescreen failures along with screen failures in renamed section.	Formatting change to align Prescreening criteria with eCRFs
Section 5.1 Inclusion Criteria	Specified that participants must meet prescreening criteria to be included in the study	Editorial change for clarification regarding participants’ inclusion in the study.
Synopsis Section 1.2 Schema Section 5 Study Population Prescreening (criterion #P2)	Added text indicating prescreening should be started as soon as possible, prior to completion of adjuvant therapy.	Editorial changes for clarification in study conduct.
Section 5.2 Exclusion Criteria (criterion #2)	Added text regarding ovarian suppression treatment as a permitted medication.	Editorial change for consistency with rest of protocol.
Synopsis Section 5.2 Exclusion Criteria (criterion #4) Appendix 1 Exclusion of Participants Who Have Shown No Definitive Response to Preoperative Chemotherapy	Clinical evaluation added as criteria for evaluation of no definitive response and additional information added for evaluation of no definitive response criteria	Clarification for study conduct. Text updated to clarify methods for assessment of no definitive response with no impact on participant safety, study conduct, or study interpretation.
Section 1.2 Study Schema, Figure 2	Key eligibility criteria updated	Administrative change to align with protocol text.
Section 1.2 Schema, Figure 1 Section 1.3 Schedule of Activities, Table 2 Prescreening Section 4.1 Overall Design	Changed "final cycle" for initiation of prescreening platform to "last 6 weeks of chemotherapy and radiation adjuvant treatment" in notes/footnotes.	Editorial change to provide clarification with a measurable time definition for specific adjuvant treatment.
Section 1.3 Schedule of Activities Table 2 (Prescreening)	Included note regarding regimen stability for HR+ participants in	Formatting/editorial clarification for study conduct to align with protocol text

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities, Table 3	Cohort 1 on endocrine therapy. Updated note for pathology report to indicate it will accompany samples sent for testing. Assessments added to Prescreening activities (eligibility; demography; disease characteristics; anticancer, radiation therapies; surgical procedures for current indication prior to Screening; and AEs). Similarly, activities related to Demography, disease characteristics, and tumor characteristics removed from Table 3, anticancer therapies updated to clarify only prior anticancer therapies for historical cancers, and notes updated. Medical history notes updated to outline information to be captured.	and intended data collection for screening versus prescreening periods, and analysis. There is no change to the information collected as part of the clinical study; this change only represents a clarification of when the data are collected, i.e., no impact on safety and no significant impact on study conduct, or study interpretation.
Section 1.3 Schedule of Activities, Table 3 Section 8.4.6 Pregnancy Testing Appendix 2 Clinical Laboratory Tests, Table 18 Appendix 4 Contraceptive and Barrier Guidance	Notes and text requiring serum pregnancy testing adjusted and footnote removed in Table 18 (previously Table 17).	Clarification for consistency in study conduct regarding pregnancy testing requirements.
Section 1.3 Schedule of Activities, Table 3 Section 8.8.1 Tumor Tissue Collection at Time of Disease Recurrence	Added footnote and text indicating optional biopsies must be performed before initiating new anticancer therapy and do not need to occur within 7-days of last dose.	Editorial change to provide clarification for study conduct.
Section 1.3 Schedule of Activities, Table 3 Section 8.9 Patient Reported Outcome Measures Section 8.9.5 Patient Global Impression Items	Updated note for PRO collection to be completed on the assigned clinic visit day and for PGIC to indicate it will be collected starting on Cycle 2/Day 1 and every 28 days thereafter.	Editorial change to provide clarification for study conduct.
Section 1.3 Schedule of Activities Table 2 (Disease Characteristics) Table 3 (Eligibility)	Included note regarding recurrence during prescreening/screening and information to be collected.	Editorial change to provide clarification for study conduct.
Section 1.3 Schedule of Activities Table 3	Updated notes to specify difference in visit windows for monthly versus weekly visits.	Editorial clarification for study conduct.
Section 1.3 Schedule of Activities Table 3 Section 8.3.1 Postbaseline Imaging and Tumor Assessment	Text regarding CT or MRI for DFS updated to include: (Year 1 Weeks 12, 24, 36, 48; Year 2, Weeks 60, 72, 84, 96) and notes updated regarding PET scan,	Editorial clarification for the Investigator.

Section # and Name	Description of Change	Brief Rationale
	and that imaging should continue within the defined interval windows.	
Section 1.3 Schedule of Activities Table 3	Note added to anticancer therapy following study treatment indicating any new anticancer treatment started before the Safety Follow-up Visit must be collected during this visit as outlined in eCRF completion instructions.	Administrative change for omission in the original protocol for the evaluation of the safety of niraparib in this population.
Section 1.3 Schedule of Activities, Table 3	Hematology and clinical chemistry blood draw visit windows for specific visits added to notes.	Editorial clarification for study conduct providing flexibility in blood draws.
Section 1.3 Schedule of Activities, Table 3	Clarified that assessments for ctDNA CCI [redacted]	Editorial change to align with protocol text.
Section 1.3 Schedule of Activities, Table 3 (Niraparib or placebo dispensed/collected)	Note added regarding recording missed doses.	Editorial change to align with data collection in eCRFs.
Section 1.3 Schedule of Activities, Table 4 PK Sampling Schedule for All Participants	Removed text regarding holding dose 1 day prior to Cycle 2/Day 1	Administrative change to correct error in original protocol.
Synopsis Section 4.1 Overall design Section 4.2 Overall Rationale for Study Design Sections 8.8 Translational Research Section 9.3.2 Interim Analysis	Included name of assay for tumor *BRCA*/HRD testing.	Administrative change for clarification for study conduct and for regulatory/ethics approval of the assay as part of the current protocol and any necessary reporting requirements related to assay use in this study.
Section 6.8 Concomitant Medications and Nondrug Therapies	Concomitant medication follow-up corrected to indicate that it continues until the Safety follow-up visit after end of treatment and not until end of study.	Administrative change to provide clarification for study conduct.
Section 4.1 Overall Design Section 8.1.1 General Guidance for Treatment Continuity When Participants Are Unable to Come into the Clinic, Table 14 Section 8.6 Pharmacokinetics	Updated to include at-home nursing services (or local laboratory/clinic) and clarification of study days for these visits if participants are unable to attend clinic visits.	Administrative change to provide clarification for participants' safety during the COVID-19 pandemic.
Section 1.3 Schedule of Activities, Table 2 Prescreening Section 8.8 Translational Research	Adjusted protocol text to refer to Study Reference Manual for details.	Editorial change to provide clarification of tissue requirements per vendor performing the analysis outlined in the study reference manual.
Section 2.2.2 Treatment Options for Patients with Operable HER2− Breast Cancer Section 2.2.4 PARP Inhibitors Section 2.2.5.2 Efficacy of Niraparib in Breast Cancer (Study 3000-PN162-01-001	CCI [redacted]	

Section # and Name	Description of Change	Brief Rationale
TOPACIO) Section 2.2.5.4 Niraparib and Pembrolizumab Section 2.2.6 Circulating Tumor DNA Section 2.3.2 Benefit Assessment Section 2.3.3 Overall Benefit/Risk Conclusion Section 4.2 Scientific Rationale for Study Design	CCI [redacted]	
Section 4.3 Justification for Dose	Amended language for niraparib dosing in participants with moderate hepatic impairment.	Administrative change to align with the IB.
Section 6 Study Treatments and Concomitant Therapy	Updated references to Pharmacy Manual to Study Reference Manual	Administrative change to correction text throughout protocol as study does not have a Pharmacy Manual.
Section 6.1.1 Niraparib	Text corrected regarding tablets provided for dosing with up to 3 days flexibility.	Administrative change to correction text and align with Table 3 visit window.
Section 6.1.1 Niraparib, Table 10	Updated footnotes regarding hepatic impairment definitions.	Editorial change to provide clarification for participant safety.
Section 6.1.1 Niraparib	Included text that dose escalation not permitted once initial starting dose is assigned.	Editorial change for clarification of study conduct.
Section 6.3.1 Randomization	Removed IVRS and reference to phone numbers.	Editorial change to correction align protocol text regarding randomization procedures being used in the study.
Section 6.3.3 Blinding and Breaking the Blind	Deleted text regarding unblinded third party not relevant to the study.	Editorial change to correct text to align with study.
Synopsis Section 4.1 Overall Design Section 7.1 Withdrawal/Stopping Criteria	Updated text regarding duration of treatment.	Editorial clarification for study conduct.
Section 7.1 Withdrawal/Stopping Criteria	Updated text regarding withdrawal of participants with additional primary malignancies other than MDS and AML and regarding possibility of continued niraparib treatment if participants are discontinued.	Editorial change for clarification
Synopsis Section 7.3.1 Further Biomedical Research Maintaining Confidential Participant Information	Clarification that Further Biomedical Research is after study completion.	Administrative change to align with ICF text.
Synopsis	Clarification regarding possible	Editorial changes for clarification

Section # and Name	Description of Change	Brief Rationale
Section 8.8 Translational Research Appendix 9 Use/Analysis of DNA	use of tumor tissue and blood samples for exploratory research. Appendix heading updated and clarified DNA samples can be derived from tumor or blood specimens.	
Section 8.1.1 General Guidance for Treatment Continuity When Participants Are Unable to Come into the Clinic Section 8.1.1, Table 14	Removed text pertaining to global telemedicine and updated Table 14 (previously Table 13) table title for clarification.	Editorial changes for Clarification that Sponsor not providing global telemedicine services; sites to engage their own local platform.
Section 8.1.1.1 Direct to Participant Investigational Medicinal Product Shipments	Revised text to remove drug supply vendor name.	Administrative correction.
Section 8.5 Adverse Events, Serious Adverse Events, and Other Safety Reporting Appendix 5 Regulatory, Ethical, and Study Oversight Considerations	Removed mention of LAR.	Administrative change to align with inclusion criterion 13.
Section 8.5.6 Cardiovascular and Death Events	Clarification regarding the recording of death information in eCRFs.	Administrative change to provide clarification for collection of death information aligned with eCRFs.
Section 8.7 Genetics	Updated section heading and language regarding WES testing.	Administrative change to provide clarification in protocol text.
Section 9.4.5.1 Pharmacokinetic Parameters	Clarifications in PK language and GSK analysts access to PK datasets.	Administrative change to align with PK and Exposure-Response Analysis Plan as per regulatory agency recommendation and for clarification on access to data.
Appendix 3 Guidelines for Assessment of Disease, Disease Progression and Response Criteria	Updated criteria for participants with no evidence of disease at baseline.	Editorial changes to provide clarification for study conduct.

Amendment DEU-2: (10 Sep 2021)

Overall Rationale for the Amendment

Amendment DEU-2 is a country-specific protocol amendment in response to Health Authority feedback to align protocol text with country regulatory requirements as outlined below.

Summary of Changes for Amendment DEU-2:

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1 General Guidance for Treatment Continuity When Participants Are Unable to Come into the Clinic Section 8.5 Adverse Events, Serious Adverse Events,	Removed ’24 hours’ from the definition of immediate reporting of SAEs	To align with the German GCP regulation (Section 12 (4)) which states that the Investigator must inform the sponsor immediately of the occurrence of a serious adverse event without mention of an acceptable duration.

Section # and Name	Description of Change	Brief Rationale
and Other Safety Reporting Appendix 8 AEs And SAEs: Definitions And Procedures For Recording, Evaluating, Follow-Up, And Reporting		

Amendment DEU-1: (26 Jul 2021)

Overall Rationale for the Amendment

Amendment DEU-1 is a country-specific protocol amendment in response to Health Authority feedback to align protocol text with country regulatory requirements as outlined below.

Summary of Changes for Amendment DEU-1:

Section # and Name	Description of Change	Brief Rationale
Section 8.5 Appendix 5 Regulatory, Ethics, and Study Oversight Considerations	Removed mention of legally authorized representative (LAR).	To align with inclusion criterion 13 and regulatory feedback (LAR not permitted under the German Medicines Act).

Amendment GBR-1: (30 Apr 2021)

Overall Rationale for the Amendment

Amendment GBR-1 is a country-specific amendment to the original version of the protocol and was produced to amend protocol language pertaining specifically to COVID-19 vaccination and contraceptive use as noted during Health Authority review.

Summary of Changes for Amendment GBR-1:

Section # and Name	Description of Change	Brief Rationale
Headers, cover page, Protocol Amendment Summary of Changes, and throughout	Headers and cover page were updated with new version number; headers were updated with new document number; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment. Editorial changes made throughout.	Editorial changes to align with the Sponsor's standard protocol template and ways of working and inclusion of specific language noted during Health Authority review
Section 5.1 (Inclusion criteria number 12); Appendix 4, Table 19	Recommendations for duration of contraception use for male participants was updated to continue for 90 days, rather than 180 days, after the last dose of study treatment.	Protocol has been amended to align with the niraparib Investigator's Brochure.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 (Exclusion criteria number 9); Section 6.8.1 (Prohibited medications)	*Deleted language:* The use of live Corona virus disease 2019 (COVID-19) adenoviral vaccines within 30 days of randomization must be discussed with the GSK Medical Monitor. *Added language:* Study participants can be vaccinated against COVID-19 using vaccines authorized via the appropriate regulatory mechanisms (i.e. Emergency Use Authorization, Conditional Marketing Authorization or Marketing Authorization Application). Note: mRNA and adenoviral-based COVID-19 vaccines are considered nonlive.	Updated recommendation on use of COVID-19 vaccines based on GSK Guidance to reflect current evolving medical practice.

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