| **Information Type:** | Statistical Analysis Plan (SAP) |
|---|---|

# TITLE PAGE

| | |
|---|---|
| **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) |
| **Study Number:** | 213831 |
| **Compound Number:** | Niraparib (GSK3985771) |
| **Abbreviated 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 |
| **Acronym:** | ZEST |

**Sponsor Name:** GlaxoSmithKline Research & Development Limited

**Regulatory Agency Identifier Number(s)**

| **Registry** | **ID** |
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| IND | 117580 |
| EudraCT | 2020-003973-23 |
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# VERSION HISTORY

The Statistical Analysis Plan (SAP) for study 213831 is based on the amended (Amendment 04) protocol approved 28-Nov-2023.

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| SAP | 16 Jun 2021 | Original Protocol (25-Jan-2021) | Not Applicable | Original version |
| SAP Amendment 01 | 01Feb2024 | PA04 (28-Nov-2023) | Objectives/End point | Protocol Amendment |
| SAP Amendment 02 | 23 Jul 2024 | PA04 (28-Nov-2023) | Updates/clarifications based on data (dose interruption, drug accountability, actual dose), update to disease characteristics table, Hy's law update to align with protocol, update to EOS to align DCO definition as directly from protocol | Preparation for CSR |

# INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the synoptic Clinical Study Report (CSR) for Study 213831 (ZEST). Details of the planned final analysis to support the primary endpoint are provided. There are no secondary endpoints for this study.

A supplementary plan may be created for exploratory analyses (such as circulating tumor DNA (ctDNA) dynamics, biomarker and efficacy analyses), and analyses to support publications.

## 1.1. Objectives, Estimands and Endpoints

### 1.1.1. Objectives and Endpoints

The safety and tolerability of niraparib is being assessed as the primary endpoint and will use the Safety (SAF) Population. There are no secondary endpoints. The exploratory endpoints may be explored in a supplementary plan.

**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 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:<br>• 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 |

| Objectives | Endpoints |
|---|---|
| | • Initiation of a new systemic anticancer therapy for cancer pain progression or worsening of disease-related symptoms<br>• 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]). |
| 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];) |
| CCI [redacted] | |

### 1.1.2. Estimands

The primary study objective is the evaluation of safety and tolerability of niraparib. Estimands are not applicable for the primary endpoint.

## 1.2. Study Design

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 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.

As a result of an 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 are managed as outlined in Protocol Amendment 04 Table 12.

According to Protocol Amendment 04 (Section 1.1), "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 the last participant consents to Protocol Amendment 04 (or withdraws) or meets any protocol-defined stopping criteria (Protocol Amendment 04, 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."

For more details regarding the PACT Phase, refer to Protocol Amendment 04 Section 6.7.1.

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.

Once the PACT Phase is complete, and the study has ended (the last visit of the last participant in the study or last scheduled procedure for the last participant in the study), a PACT Phase Report will be produced.

| **Overview of Study Design and Key Features** | |
|---|---|
| **Design Features** | • Design: This study was previously designed as a multicenter, multicohort, Phase 3, double-blinded, placebo-controlled study comparing the safety and efficacy of niraparib to placebo in patients 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.<br>• A decision was made by the Sponsor to permanently discontinue enrollment into the ZEST study, which was communicated on 25 April 2023 (i.e., the date of the decision to stop enrollment) and the study was centrally unblinded.<br>• The total duration of study participation began with the signing of the informed consent form (ICF) through the participants' last study procedure (as outlined in the Schedule of Activities (SOA) Protocol Amendment 04, Section 1.3).<br>• For the participants who meet all eligibility criteria and are randomized within the study to active treatment, the maximum duration of treatment with niraparib is until the patient meets the stopping criteria as outlined in Protocol Amendment 04, Table 12. |

| Overview of Study Design and Key Features | |
|---|---|
| | • Per Protocol Amendment 04, "Once the last participant consents to Protocol Amendment 04 (or withdraws) or meets any protocol-defined stopping criteria (Protocol Amendment 04, Section 7), the study will transition to the PACT Phase." |
| **Study Intervention** | • Niraparib will be administered orally once a day, continuously throughout each 28-day cycle starting on Cycle 1/Day 1.<br>• Placebo was administered orally once a day, continuously throughout each 28-day cycle starting on Cycle 1/Day 1 until the communication of the sponsor's decision to permanently stop enrollment into the ZEST study and to centrally unblind.<br>• Dose levels, interruptions, and reductions of niraparib should be implemented according to the guidelines as outlined in Protocol Amendment 04 Section 6.4. |
| **Study Intervention Assignment** | • As of the date of decision to stop enrolment, no further randomizations were approved by the Sponsor.<br>• There were 40 participants randomized in a 1:1 ratio following a confirmed detectable ctDNA test result, central confirmation of t*BRCA*mut status, and no evidence of overt recurrent/metastatic disease to receive either niraparib or placebo.<br>• Participants were randomized based on recruitment site region, and stratified based on the following factors:<br>– Participants identified as Cohort 1 (t*BRCA*mut/HER2−) were stratified by time from last intervention* to randomization (<6 months versus ≥6 months), hormone receptor (HR) status (positive versus negative), and prognostic stage of breast cancer (Stage I/II versus Stage III)<br>– Participants identified as Cohort 2 (t*BRCA*wt/TNBC) were stratified by time from last intervention* to randomization (<6 months versus ≥6 months), prior use of adjuvant capecitabine (yes versus no), and prognostic stage of breast cancer (Stage I/II versus Stage III)<br>* Time of last intervention is defined as the date of most recent applicable oncological curative intent surgery, date of last adjuvant chemotherapy, or date of last radiotherapy fraction, whichever occurred later. |
| **Interim Analysis** | CCI [redacted] |
| **Multiplicity** | • Multiplicity adjustments are not applicable as there is no formal hypothesis testing for the primary endpoint. |

# 2. STATISTICAL HYPOTHESES

There are no formal statistical hypotheses that correspond to the final analysis as the primary endpoint is the evaluation of safety and tolerability of niraparib.

## 2.1. Multiplicity Adjustment

There are no multiplicity adjustments that correspond to the final analysis as the primary endpoint is the evaluation of safety and tolerability of niraparib.

# 3. ANALYSIS SETS

| Analysis Set | Definition / Criteria | Analyses Evaluated |
|---|---|---|
| Intent-to-Treat (ITT) | • The ITT analysis set will consist of all randomized participants whether or not randomized treatment was administered.<br>• This population will be based on the treatment and strata to which the participant was randomized and will be the primary population for the analysis of the exploratory efficacy data.<br>• Any participant who receives a treatment randomization number will be considered to have been randomized.<br>• This may be used for exploratory analysis. | • Study Population<br>• Exploratory |
| All Screened | • The All Screened analysis set will consist of all participants who sign the main study ICF to participate in the clinical study.<br>• This may be used for screen failure summaries and exploratory analysis. | • Screen Failure<br>• Exploratory |
| All Pre-Screened | • The All Pre-Screened analysis set will consist of all participants who sign the ctDNA pre-screening study ICF consenting to collection of tumour tissue samples for ctDNA assay design and t*BRCA*, homologous recombination deficiency (HRD) testing and blood samples for ctDNA testing.<br>• This may be used for pre-screen failure summaries and exploratory analysis. | • Pre-Screen Failure<br>• Exploratory |
| Safety (SAF) | • The SAF analysis set will consist of all randomized participants who receive at least 1 dose of study treatment (niraparib or placebo).<br>• Participants will be analyzed as treated.<br>• This may be used for safety (primary endpoint) and exploratory analysis. | • Safety |

# 4. STATISTICAL ANALYSES

## 4.1. General Considerations

### 4.1.1. General Methodology

The SAF population will be the primary analysis population for the primary endpoint safety analyses. The ITT population is the primary analysis population for the exploratory efficacy analysis, if evaluated.

Confidence intervals (CI) will use 95% confidence levels unless otherwise specified.

Demographic and baseline characteristics will be summarized.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum.

Categorical data will be summarized as the number and percentage of participants in each category.

Cohorts will be pooled for analyses.

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

### 4.1.2. Baseline Definition

For all endpoints, unless otherwise specified, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. For participants who did not receive study treatment during the study, baseline will be defined as the latest, non-missing collected value.

### 4.1.3. End of Study Definition

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.

According to Protocol Amendment 04 (Section 1.1), “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 the last participant consents to Protocol Amendment 04 (or withdraws) or meets any protocol-defined stopping criteria (Protocol Amendment 04, 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.”

Also per Protocol Amendment 04 (Section 1.1), "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."

All data up to the time of final DCO 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.

### 4.1.4. Multicenter Studies

In this multicenter global study, enrollment will be presented by country and site.

Since accrual was 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, and summaries of data by center will not be provided.

### 4.1.5. Durations

Durations (e.g., the duration of an adverse event [AE], etc.) are calculated as the stop date minus the start date plus one, unless otherwise specified.

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

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

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

### 4.1.6. Measures to Minimize Bias

#### 4.1.6.1. Randomization

As of the date of the decision to permanently stop enrollment, no additional randomization requests were approved by the sponsor.

All participants were centrally randomized using an Interactive Web Response System (IWRS). Before the study was initiated, the log in information and directions for the IWRS was provided to each site.

Randomization was conducted by region and according to stratification factors described in Section 4.1.6.3.

Cohorts are pooled for further analyses unless otherwise specified.

#### 4.1.6.2. Blinding

ZEST was originally designed as a double-blind study. As of the date of the decision to stop enrollment, no additional randomization requests were approved by the Sponsor and the study was centrally unblinded.

#### 4.1.6.3. Stratification

At the time of Cohort 1 participants (t*BRCA*mut/HER2−) randomization, participants were stratified based on the following factors:

- Time from last intervention* to randomization (<6 months versus ≥6 months)
- HR status (Positive versus Negative)
- Prognostic stage of breast cancer at screening (Stage I/II versus Stage III)

At the time of Cohort 2 participants (t*BRCA*wt/TNBC) randomization, participants were stratified based on the following factors:

- Time from last intervention* to randomization (<6 months versus ≥6 months)
- Prior use of adjuvant capecitabine (Yes versus No)
- Prognostic stage of breast cancer at screening (Stage I/II versus Stage III)

* Time of last intervention is defined as the date of most recent applicable oncological curative-intent surgery, date of last adjuvant chemotherapy, or date of last radiotherapy fraction, whichever occurred later. See Section 6.2.5 for applicable definitive therapies that contribute to the intervention definition.

## 4.2. Primary Endpoint Analyses

The primary endpoint is the evaluation of safety and tolerability of niraparib.

### 4.2.1. Definition of Endpoint

Safety will be evaluated based on the incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs). TEAEs leading to death, TEAEs leading to dose modifications, and TEAEs leading to discontinuation will be assessed. Clinically relevant laboratory parameters, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and use of concomitant medications will be collected and evaluated.

### 4.2.2. Main Analytical Approach

The SAF population will be used for the analysis of safety data.

All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities coding system (MedDRA). The severity of AEs will be graded utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

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.

#### 4.2.2.1. Extent of Exposure

The number of participants administered study treatment will be summarized according to the time on study.

The frequency and percentage of participants who have a niraparib dose reduction, and dose interruption will be summarized.

Dose interruptions are calculated based on the missed assessment dose from the Continual Dosing Details on the treatment exposure eCRF.

Dosing information, as well as derived exposure parameters, will be presented for each participant in the form of data listings.

Actual dose will be calculated based on the data collected from the treatment exposure data via the eCRF.

The following exposure parameters as defined in Table 2 will be summarized descriptively for treatment.

**Table 2 Exposure Parameters**

| Parameter | Definition |
|---|---|
| Time on Study Treatment | Time on study drug that does not exclude interruptions |
| Subject Daily Dose | The cumulative actual dose divided by the duration of exposure |
| Population Daily Dose | A dose on each day is treated as an observation and the summary statistics are based on the dose on each individual day |
| Cumulative Actual Dose | The sum of all actual study drug doses consumed. |

#### 4.2.2.2. Adverse Events and Serious Adverse Events

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

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 start of new anticancer therapy.

Events will be summarized by frequency and proportion of total participants, and by SOC and preferred term (PT).

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.

When summarizing AEs by maximum grade, the following algorithms for counting the participant will be applied:

- PT row: Participants experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- SOC term row: Participants experiencing the same AE SOC several times with different grades will only be counted once with the maximum grade.
- Any event row: Each participant with at least one AE will be counted only once at the maximum grade no matter how many events they have.
- Participant will be counted once per SOC, PT or any event row for the AE summaries without grades, unless specified.
- The relationship of each AE to the study treatment will be summarized as assessed by the Investigator.
- A study treatment-related AE is defined as an AE for which the Investigator classifies the relationship to niraparib as RELATED. A worst-case scenario approach will be taken to handle missing relatedness data, i.e., the summary table will include events considered RELATED to niraparib or with missing relationship for study treatment.

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.

All TEAEs, whether serious or non-serious, will be reported on from the start of treatment until 30 days after the last dose of study treatment until the participant withdraws consent for study participation, or until the participant starts subsequent anticancer therapy, whichever (applicably) occurs first.

The following summary tables will be provided:

- Treatment-Emergent Adverse Events
  - All Adverse Events Overview
  - All Adverse Events by SOC and PT
  - All Adverse Events by SOC and PT and Maximum Grade (1,2,3,4,5,3-5)
  - All Grade 3-5 Adverse Events by SOC and PT
  - Drug-Related Adverse Events by SOC and PT
  - Drug-Related Adverse Events by SOC and PT and Maximum Grade (1,2,3,4,5,3-5)
  - Grade 3-5 Drug-Related Adverse Events by SOC and PT
  - Adverse Events Leading to Permanent Discontinuation of Study Drug by SOC and PT
  - Adverse Events Leading to Drug Interruption by SOC and PT
  - Adverse Events Leading to Dose Reduction by SOC and PT
  - Non-Serious Drug-Related Adverse Events by Overall Frequency
  - Non-Serious Adverse Events by SOC and PT (Number of Occurrences)
  - Adverse Events Leading to Death by SOC and PT
- Serious Treatment-Emergent Adverse Events
  - Serious Adverse Events by SOC and PT
  - Serious Adverse Events by SOC and PT and Maximum Grade (1,2,3,4,5,3-5)
  - Drug-Related Serious Adverse Events by SOC and PT
  - Drug-Related Serious Adverse Events by SOC and PT and Maximum Grade (1,2,3,4,5,3-5)
  - Serious Adverse Events by SOC and PT (Number of Occurrences)
  - Serious Fatal and Non-Fatal Drug-Related Adverse Events by PT

The incidence of deaths and the primary cause of death will be summarized (Section 4.2.2.4).

#### 4.2.2.3. Adverse Events of Special Interest

The following will be considered AESIs (serious or non-serious) for the purpose of analyses:

- Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)
- Second primary cancers (new malignancies other than MDS or AML)

Table 3 outlines the AESIs with the criteria of mapping MedDRA PTs for each AESI using Standardized MedDRA Queries (SMQs), High Level Terms (HLTs), and/or PTs.

The list of PTs corresponding to AESIs is provided in a separate document (Section 6.4).

Events will be summarized by frequency and proportion of total participants, and by AESI Group Category and PTs (Section 6.4).

**Table 3 Adverse Events of Special Interest**

| Group Term | MedDRA Criteria for Selection of Preferred Terms |
|---|---|
| AESI: MDS/AML event | Myelodysplastic syndrome SMQ (Narrow)<br>Leukaemias acute myeloid (HLT) |
| AESI: Malignant tumour SMQ (other than MDS/AML) | Haematological malignant tumors SMQ (Narrow),<br>Non-haematological malignant tumors SMQ (Narrow) |

The following summary tables will be provided for Treatment-Emergent AESI's:

- Adverse Events of Special Interest by Group Category and PT
- Drug-Related Adverse Events of Special Interest by Group Category and PT
- Adverse Events of Special Interest Leading to Permanent Discontinuation of Study Drug
- Serious Adverse Events of Special Interest by Group Category and PT

#### 4.2.2.4. Deaths

All deaths will be summarized based on the frequency and percentage of participants. This summary will classify participants by time of death relative to the last dose of medication (>30 days, or ≤30 days) and will summarize the primary cause of death. A supportive listing will be generated on participants who died.

#### 4.2.2.5. Pregnancy

Any pregnancies that occur within 180 days post-treatment will be reported.

If participants become pregnant while on the study, the information will be included in the narratives.

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 (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and will be reported as such.

#### 4.2.2.6. Laboratory Data

Laboratory evaluations including the analyses of chemistry, and haematology laboratory tests and other screening tests will be based on GSK Core Data Standards.

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

A summary of worst-case laboratory results by maximum grade increase post-baseline relative to baseline, and a summary of worst-case results relative to normal range post-baseline relative to baseline will be provided for hematology and chemistry lab tests that are gradable by CTCAE v5.0. These summaries will display the frequency and percentage of participant with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia separately.

A listing of all laboratory data will be provided (including values outside of normal range).

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

Summaries of hepatobiliary laboratory events including possible Hy’s law cases will be provided in addition to what has been described above. Possible Hy’s law cases are defined as any elevated alanine aminotransferase (ALT) ≥3×upper limit of normal (ULN), and total bilirubin≥2×ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and INR > 1.5, if INR measured. Total bilirubin≥2×ULN can be within 28 days following the ALT elevation and if direct bilirubin is available on the same day, it must be ≥ 35% of total bilirubin. The summary will be produced for worst case post baseline only.

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

#### 4.2.2.7. Vital Signs

Values of vital signs (temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure) as well as the change from baseline will be summarized by scheduled visit using n, mean, median, std, minimum and maximum.

A summary of worst-case vital signs results relative to potential clinical importance criteria post baseline relative to baseline will be presented.

The determination of the worst-case post baseline vital signs will consider both planned and unscheduled assessments. Participants with missing baseline values are assumed to have a normal baseline value. The percentages are based on the number of participants in the treatment group with baseline and post-baseline data.

#### 4.2.2.8. Performance Status

A summary of change in ECOG performance from baseline will be provided.

#### 4.2.2.9. Cardiovascular Risk Factors

A summary of family history of cardiovascular risk factors presenting frequency of premature coronary artery disease. A summary of substance use will also be provided.

#### 4.2.2.10. Concomitant Medications

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

Concomitant medications include any medication that was taken on-study.

## 4.3. Secondary Endpoint Analyses

Not applicable as there are no secondary endpoints.

## 4.4. Exploratory Endpoints Analyses

A supplementary plan may be created for exploratory analyses (such as ctDNA dynamics, biomarker, genetics, and efficacy analyses) and reported separately from the main CSR.

### 4.4.1. Subgroup Analyses

There are no planned subgroup analyses.

### 4.4.2. BICR

A blinded independent central review (BICR) is no longer applicable for this study. Available BICR data may be used for exploratory analyses and will be defined in a separate plan.

### 4.4.3. IDMC

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.

## 4.5. Interim Analyses

CCI

[redacted]

## 4.6. Changes to Protocol Defined Analyses

There were no changes from the originally planned statistical analysis specified in Protocol Amendment 04.

# 5. SAMPLE SIZE DETERMINATION

As of the date of the decision to stop enrollment, no additional randomization requests were approved by the Sponsor. A total of 40 participants were randomized in the study. The sample size determinations were based on the original ZEST study design and endpoints. The sample size determination aligned with the original protocol is *italicized* below and is as followed:

*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 gBRCAmut HER2− breast cancer (OlympiAD study: 19 months [Robson, 2017]; EMBRACA study: 22 months [Litton, 2018].*

CCI

[redacted]

*Cohort 1 (tBRCAmut/HER2−):*

CCI

*Cohort 2 (tBRCAwt/TNBC):*

CCI

CCI

[redacted]

# 6. SUPPORTING DOCUMENTATION

## 6.1. Appendix 1: Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the ITT Analysis Set.

### 6.1.1. Participant Disposition

A summary table will include the number of participants who entered pre-screening (signed the pre-screening ICF), screening (signed the main ICF), and were randomized will be provided. Reasons for pre-screen failure, and screen failure will be provided.

A summary of the frequency and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized.

A summary of study intervention status will be provided. This display will show the number and percentage of participants who have completed the scheduled study intervention, are ongoing with study intervention, or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention.

Listings of reasons for study and treatment withdrawal will be provided.

### 6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including descriptive statistics will be summarized based on the ITT analysis set:

- Age at randomization (continuous, and age categories: 18-64, 65-84, >=85 )
- Gender
- Ethnicity
- Height/Weight at screening
- Race

A summary of disease characteristics will be provided. This summary will include, and not limited to, Table 4.

**Table 4 Disease Characteristics of Current Indication**

| Disease Characteristic | Categories (if applicable) |
|---|---|
| Primary Tumor Type (Section 6.2.1 ) | ER+/PR+, ER+/PR-, ER-/PR+ TNBC |
| BRCA Status (Section 6.2.2) | Mutant, Wild Type, Missing(if applicable) |
| HRD Status | HRd, HRp, Not Determined |
| Histology at Initial Diagnosis | All non-zero categories displayed in the eCRF |
| Stage at Initial Diagnosis (Section 6.2.3) | I, II, III |
| Concurrent Hormone Endocrine Therapy at Randomization (Section 6.2.4) | Yes, No |
| Time since initial diagnosis at randomization (Section 4.1.5) | <18 months, ≥ 18 months |
| Time from last intervention at randomization (Section 4.1.5; Section 6.2.5) | <6 months, ≥ 6 months |

### 6.1.3. Prior and Current Medical Procedures

A summary of prior and current medical procedures will be provided and presented by classification and frequency.

### 6.1.4. Prior and Current Surgical Procedures

A summary of prior and current surgical procedures will be provided and presented by classification and frequency.

### 6.1.5. Prior Anti-Cancer Therapies

A summary of prior anticancer therapy (for non-current indication) , a summary of prior adjuvant and neo-adjuvant anticancer therapy (for current indication), and a summary of prior radiation therapy (for non-current and current indication) will be presented by frequency.

The single line of curative therapy is defined as a curative treatment or regimen of treatments given curatively, as recorded in the eCRF.

### 6.1.6. Study Intervention Compliance

A summary of overall compliance for treatment based on the exposure data will be produced. Overall compliance will be summarized using descriptive statistics as well as the categories <80%, 80%-105%, and >105%.

Study intervention Compliance (%) = [Total cumulative actual dose / Total cumulative scheduled dose] *100.

Listings of exposure data will also be provided.

### 6.1.7. Additional Analyses Due to the COVID-19 Pandemic

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

## 6.2. Appendix 2: Data and Terminology Definitions

### 6.2.1. Primary Tumor Type

The primary tumor type is categorized as ER+/PR+, ER+/PR- , ER-/PR+ and TNBC. These categories are defined below:

- ER+/PR+
  - Estrogen Receptor (ER) Status = Positive
  - Progesterone Receptor (PR) Status = Positive
  - HER2 Status = Negative
- ER+/PR-
  - ER Status = Positive
  - PR Status = Negative
  - HER2 Status = Negative
- ER-/PR+
  - ER Status = Negative
  - PR Status = Positive
  - HER2 Status = Negative
- TNBC
  - ER Status = Negative
  - PR Status = Negative
  - HER2 Status = Negative

### 6.2.2. BRCA status

BRCA status should be categorized based on the results from the central testing conducted by the external vendor.

BRCA status is categorized as Wild-Type, BRCA mutant, or Missing and defined by the following:

Mutant:

- If the participant had central BRCA testing conducted, had BRCA1 or BRCA2 variant detected, and the variant interpretation is either “Positive for Deleterious Mutation" or “Suspected for Deleterious Mutation”, then the participant is categorized as BRCA “Mutant”.

Wild-Type:

- If the participant had central BRCA testing conducted, and did not have BRCA1 or BRCA2 variant detected, then the participant is categorized as BRCA “Wild-Type”.
- If the participant had local BRCA testing conducted, had BRCA1 or BRCA2 variant detected, and the variant interpretation is either “Genetic Variant of Unknown Significance” or “Uncertain” or “No Deleterious Mutation Found”, then the participant is categorized as BRCA “Wild-Type”.

Missing:

- If the participant did not have central BRCA testing conducted, then the participant is categorized as BRCA “Missing”.
- If the participant had central BRCA testing conducted, but has no details on the (“blank” BRCA1 and “blank” BRCA2) variant detected, then the participant is categorized as BRCA “Missing”.

### 6.2.3. Staging

The staging described in these analyses will be based on the (prior) adjuvant and neo-adjuvant anticancer therapy for current indication. More specifically,

- For a participant that received Neoadjuvant therapy (regardless of adjuvant therapy), clinical prognostic staging will be used to define staging as derived from AJCC for breast cancer staging criteria 8th edition.
- For a participant that received adjuvant therapy (and no neoadjuvant therapy), pathologic prognostic staging will be used to define staging as derived from AJCC for breast cancer staging criteria 8th edition.
- For a participant that received no neo-adjuvant or no adjuvant therapy then the pathological prognostic staging will be used to define staging as derived from AJCC for breast cancer staging criteria 8th edition.

Staging will be grouped as Stage 1 (inclusive of Stage 1A, Stage 1B), Stage 2 (inclusive of Stage 2A, Stage 2B), Stage 3 (inclusive of Stage 3A. Stage 3B, and Stage 3C).

### 6.2.4. Endocrine Therapy Use

Endocrine Therapy Use describes a participant who used a subset of anti-cancer therapies or concomitant medications that include (PTs):

- Anastrozole
- Letrozole
- Exemestane
- Tamoxifen/ Tamoxifen citrate
- Leuprorelin/ Leuprorelin acetate
- Goserelin / Goserelin acetate
- Triptorelin

### 6.2.5. Last Intervention

Time of last intervention of is defined as the date of most recent applicable oncological curative intent surgery, date of last adjuvant chemotherapy, or date of last radiotherapy fraction, whichever occurred later.

The list of prior therapies (PTs) for the current indication that do NOT contribute to the last intervention definition are:

- Anastrozole
- Letrozole
- Exemestane
- Tamoxifen / Tamoxifen citrate
- Leuprorelin / Leuprorelin acetate
- Goserelin / Goserelin acetate
- Triptorelin
- Pembrolizumab
- Nivolumab
- Atezolizumab
- Durvalumab
- Ipilumimab
- Zoledronic acid / Zoledronic acid monohydrate

- Estradiol
- Vagifem

The list of prior surgeries (PTs) for current indication that contribute to the last intervention definition are:

- Breast Conserving Surgery
- Simple Mastectomy
- Biopsy Lymph Gland
- Axillary Lymphadenectomy
- Radical Mastectomy

### 6.2.6. Randomized Participants Subject Status and Reasons for Discontinuation from Study and Treatment

For Participants Randomized to Niraparib:

- "Ongoing on treatment" is categorized as randomized participants with no End of Treatment visits that have occurred, and the participants are still on treatment.
- "Discontinued from treatment" is categorized as participants randomized with an End of Treatment visit that have occurred. "Reasons for Treatment Discontinuation" are categorized by the Subject Status for Study Treatment Discontinuation.
- "Ongoing on study" is categorized as randomized participants randomized with no End of Study visits that have occurred.
- "Discontinued from study" is categorized as randomized participants with an End of Study visit that have occurred. "Reasons for Study Discontinuation" are categorized by the Subject Status for Study Conclusion.

## 6.3. Appendix 3: Data Derivations Rule

### 6.3.1. Criteria for Potential Clinical Importance

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

NCI-CTCAE (v5.0.0) will be used to assign grades to the relevant laboratory parameters, blood pressure, temperature.

In addition, the following criteria will be used to flag potential clinical importance (PCI):

| Parameters | Unit | PCI Range |
|---|---|---|
| Heart Rate | bpm | <60 (L); >100 (H) |
| Temperature | C | <28 (L); > 40 (H) |
| Systolic Blood Pressure | mm | <85 (L); ≥ 160 (H) |
| Diastolic Blood Pressure | mm | <50 (L); ≥100 (H) |

### 6.3.2. Assessment Window

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

### 6.3.3. Participants with Multiple Site IDs, Investigator IDs, or Subject IDs

Participants who switch to one or more sites and/or investigators will be associated with the most recent site and/or investigator ID.

Participants who fail prescreening due to ineligibility and are not applicable for another visit can be rescreened under the same subject ID.

If a participant fails screening due to other eligibility criteria, they can be rescreened under a new subject ID.

If a participant has a negative ctDNA test result at prescreening and is eligible for another prescreening visit, they will remain under the same subject ID until no longer applicable.

Previous subject ID’s for the same participant are tracked in the eCRF and the most recent subject ID associated with a positive ctDNA test result will be used for randomization.

### 6.3.4. Multiple Measurements at One Analysis Time Point

For lab tests on a study day, if more than one assessment is taken on the same day, the test from a central lab will be taken over the test from a local lab. If multiple assessments are taken from the same type of lab, the worst case will be used.

As stated in the protocol, three readings of blood pressure and heart rate should be taken. The first reading should be rejected and the second and third averaged to give the measurement to be recorded in the eCRF.

### 6.3.5. Handling of Partial Dates

| Element | Reporting Detail |
|---|---|
| General | • Partial dates will be displayed as captured in participant listing displays.<br>• However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below.<br>• Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of AEs). |
| Adverse Events | • Partial dates for AE recorded in the eCRF will be imputed using the following conventions: |
| | Missing start day: • If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.<br>• Else if study treatment start date is not missing:<br>o If month and year of start date = month and year of study treatment start date, then<br>▪ If stop date contains a full date and stop date is earlier than study treatment start date, then set start date= 1st of month.<br>▪ Else set start date = study treatment start date.<br>o Else set start date = 1st of month. |
| | Missing start day and month: • If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.<br>• Else if study treatment start date is not missing:<br>o If year of start date = year of study treatment start date, then<br>▪ If non-missing AE stop date is unequivocally earlier than study treatment start date, then set start date = January 1.<br>▪ Else set start date = study treatment start date.<br>o Else set start date = January 1. |

| Element | Reporting Detail | |
|---|---|---|
| | Missing end day | A '28/29/30/31' will be used for the day (dependent on the month and year) |
| | Missing end day and month | No Imputation |
| | Completely missing start/end date | No imputation |
| | Note: If imputed date is greater than study end date or death date, then earliest of these dates will be used as an end date. | |
| Concomitant Medications | • Partial dates for any concomitant medications recorded in the eCRF will be imputed using the following convention: | |
| | Missing start day | • If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.<br>• Else if study treatment start date is not missing:<br>o If month and year of start date = month and year of study treatment start date, then<br>▪ If stop date contains a full date and stop date is earlier than study treatment start date, then set start date= 1st of month.<br>▪ Else set start date = study treatment start date.<br>o Else set start date = 1st of month. |
| | Missing start day and month | • If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.<br>• Else if study treatment start date is not missing:<br>o If year of start date = year of study treatment start date, then<br>▪ If stop date contains a full date and stop date is earlier than study treatment start date, then set start date = January 1.<br>▪ Else set start date = study treatment start date.<br>o Else set start date = January 1. |

| Element | Reporting Detail | |
|---|---|---|
| | Missing end day | A '28/29/30/31' will be used for the day (dependent on the month and year) |
| | Missing end day and month | A '31' will be used for the day and 'Dec' will be used for the month. |
| | Completely missing start/end date | No imputation |
| | Note: If imputed date is greater than study end date or death date, then earliest of these dates will be used as an end date. | |
| Prior Anticancer Therapy/ Radiotherapy/ Surgical Procedures | • Incomplete dates for disease history and prior anticancer therapy (e.g. initial diagnosis date, chemotherapy start/end dates) will be imputed as follows:<br>o If the day is missing, it will be imputed to the 1st day of the month.<br>o If both day and month are missing, the month and day will be imputed as January 1st.<br>o If the date is completely missing, no imputation will be performed.<br>Note: If imputed end date is earlier than the start date, then the start date will be considered as the therapy end date. | |
| Exposure End Date | • For imputation of missing exposure end date at an interim analysis when participants are still on treatment, the following conventions will be applied:<br>o Niraparib/Placebo: date of last known niraparib/placebo treatment | |

## 6.4. Appendix 4: MedDRA Preferred Terms for AESIs

The list of PTs corresponding to AESIs is provided in a separate document. This list will be provided by the GSK Safety Evaluation and Risk Management (SERM) and the Clinical group prior to DBL based on the most up-to-date MedDRA version.

## 6.5. Appendix 5: Abbreviations and Trademarks

### 6.5.1. List of Abbreviations

| Abbreviation or Specialist Term | Explanation |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| AJCC | American Joint Committee on Cancer |
| AML | acute myeloid leukemia |
| ATC | Anatomical Therapeutic Chemical |
| BICR | Blinded Independent Central Review |
| *BRCA* | breast cancer susceptibility gene |
| *BRCA* 1 | breast cancer susceptibility gene 1 |
| *BRCA* 2 | breast cancer susceptibility gene 2 |
| *BRCA*mut | breast cancer susceptibility gene mutation |
| CI | confidence interval |
| COVID19 | Corona virus disease 2019 |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | circulating tumor DNA |
| ctDNA+ | circulating tumor DNA positive |
| DBL | data base lock |
| DCO | data cut off |
| DFS | disease-free survival |
| DRFS | distant recurrence-free survival |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EOS | end of study |
| ER | estrogen receptor |
| ER+ | estrogen receptor positive |
| ER- | estrogen receptor negative |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| g*BRCA*mut | a deleterious or suspected deleterious germline mutation in the *BRCA* gene |
| GSK | GlaxoSmithKline |
| HER2 | human epidermal growth factor 2 |
| HER2− | human epidermal growth factor 2 negative |
| HLT | high level terms |
| HR | hormone receptor |
| HR− | hormone receptor negative |
| HR+ | hormone receptor positive |
| HRD | homologous recombination deficiency |
| HRd | homologous recombination deficient |
| HRp | homologous recombination proficient |
| IB | Investigator's Brochure |
| IDCFS | invasive breast cancer-free survival |
| ICF | informed consent form |
| IDFS | invasive disease-free survival |
| IDMC | Independent Data Monitoring Committee |
| ITT | intent-to-treat |
| IWRS | Interactive Web System |
| MDS | myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Events |
| OS | overall survival |
| PACT | Post-Analysis Continuing Treatment |
| PCI | Potential clinical importance |
| PD | progressive disease |
| PK | pharmacokinetic(s) |
| PR | progesterone receptor |
| PR+ | progesterone receptor positive |
| PR- | progesterone receptor negative |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| PT | preferred term |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse event |
| SAF | safety (analysis population) |
| SAP | Statistical Analysis Plan |
| SERM | Safety Evaluation and Risk Management |
| s*BRCA*mut | somatic mutation in the *BRCA* gene |
| SMQ | Standardized MedDRA Queries |
| SOA | Schedule of Activities |
| SOC | System organ class |
| std | standard deviation |
| 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 |
| CCI [redacted] | |
| TNBC | triple negative breast cancer |
| ULN | upper limit of normal |
| WHO | World Health Organization |

### 6.5.2. Trademarks

| Trademarks of the GlaxoSmithKline Group of Companies |
|---|
| None |

| Trademarks not owned by the GlaxoSmithKline Group of Companies |
|---|
| MedDRA |
| PRO-CTCAE |
| SAS |
| WHO |

# 7. REFERENCES

Coombes RC, P. K. ( 2019). Personalized Detection of Circulating Tumor DNA Antedates Breast Cancer Metastatic Recurrence. *Clin Cancer Res.*, 25(14):4255-4263.

Litton J, R. H. (2018). Abstract GS6-07: EMBRACA: A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced breast cancer and a germline BRCA mutation. *Cancer Research*, 78:GS6-07.

Robson M, I. S. (2017). Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med.* , 377(6):523-533.

Schmid P, A. S. (2018). Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med.* , 379(22):2108-2121.

Tolaney SM, Garrett-Mayer E, White J, et al. Updated Standardized Definitions for Efficacy End Points (STEEP) in Adjuvant Breast Cancer Clinical Trials: STEEP Version 2.0. *J Clin Oncol*. 2021 May:JCO-20.