PROTOCOL SYNOPSIS

A randomised, double-blind, parallel group, placebo-controlled multi-centre Phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline *BRCA1/2* mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy

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Study centre(s) and number of patients planned

The study will be conducted in approximately 25 countries world-wide. Approximately 300 centres will be initiated to randomise approximately 1320 patients. Additional countries and sites may be added dependent on recruitment rates.

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2014	III
Estimated date of last patient completed	2028	

Objectives

Primary Objective

The primary objective is to assess the effect of adjuvant treatment with olaparib on Invasive Disease Free Survival (IDFS)

Safety Objective

To assess the safety and tolerability of adjuvant treatment with olaparib

Secondary Objectives

1. To assess the effect of adjuvant treatment with olaparib on overall survival (OS)

2. To assess the effect of adjuvant treatment with olaparib on Distant Disease Free Survival (DDFS)

3. To assess the effect of adjuvant treatment with olaparib on the incidence of new invasive breast primary cancer and/or new epithelial ovarian cancer

4. To assess the effect of olaparib on patient reported outcomes using the FACIT fatigue scale and EORTC QLQ-C30 QoL scale

5. To assess efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the *BRCA* genes using variants identified with current and future germline *BRCA* mutation assays (gene sequencing and large rearrangement analysis)

Exploratory Objectives

The exploratory objectives of this study are:

1. To explore methods for estimating overall survival (OS) adjusting for the impact of confounding by subsequent therapies, specifically the control arm receiving subsequent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitors or platinum salts (to support reimbursement appraisals)

2. To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood sample derivatives (cells, plasma and protein and nucleic acid derivatives) - archival primary and post neoadjuvant tumour (mandatory*) and tumour biopsy at recurrence (optional) and blood samples at baseline, 30 days post study treatment and on disease recurrence (mandatory)

   *If tumour sample is not available, approval by Study Team for patient's entry into the trial is required.

3. To determine the frequency of and describe the nature of *BRCA* mutation/s in tumour samples and to compare this with germline *BRCA* mutation status

4. Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored tumour and blood samples

5. To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (i.e.

distribution, safety, tolerability and efficacy) to study treatments and/or susceptibility to disease (optional)

Study design

This is a randomised, double-blind, parallel group, placebo-controlled multi-centre Phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline *BRCA1/2* mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.

Patients will be randomised in 1:1 ratio to either olaparib or placebo. Randomisation will be stratified by prior neoadjuvant versus adjuvant chemotherapy and prior platinum use for breast cancer.

Eligible patients with *gBRCA* mutated high risk HER2 negative breast cancer will be randomised in the trial within a maximum of 8 weeks of completing their last treatment modality (surgery, chemotherapy or adjuvant radiotherapy). Definitive loco-regional treatment should be completed prior to randomisation into the trial including adequate breast surgery defined as:

- The inked margins of breast conservation surgery or mastectomy must be histologically free of invasive breast cancer and ductal carcinoma in situ with the exception of the posterior margin if this margin is the pectoralis major fascia or the anterior margin if this is the dermis. Patients with resection margins positive for lobular carcinoma in situ are eligible.

- Patients with breast conservation must have adjuvant radiotherapy. Patients having mastectomy should have adjuvant radiotherapy according to international guidelines (St Gallen/ASCO/ESTRO).

Adjuvant Group:

- Sentinel lymph node biopsy alone if negative or if lymph node(s) only contain micrometastases (≤2.0 mm) OR positive sentinel lymph node biopsy followed by axillary node clearance or axillary nodal radiotherapy

Neoadjuvant group:

- If sentinel lymph node biopsy before neoadjuvant chemotherapy: sentinel lymph node biopsy alone if negative or if lymph node(s) only contain micrometastases (≤2.0 mm) **OR** positive sentinel lymph node biopsy followed by axillary node clearance or axillary nodal radiotherapy following completion of neoadjuvant chemotherapy

- If sentinel lymph node biopsy after neoadjuvant chemotherapy: Sentinel lymph node biopsy alone if negative **OR** positive sentinel lymph node biopsy followed by axillary node clearance.

If a patient with conservative surgery has not had a mammogram or breast MRI within 12 months prior to randomization, then this assessment must be repeated prior to randomization.

Randomised patients will receive study treatment for up to a maximum of 12 months. All patients will have safety assessments every 2 weeks during the first month, every 4 weeks for the following 5 months and 3 monthly for the remaining 6 months of study treatment plus 30 days after its discontinuation. Following randomisation, all patients will be assessed regularly for signs, symptoms and evidence of disease recurrence by taking medical history, physical examination and mammogram/breast MRI (breast MRI preferred for patients younger than 50 years). Efficacy assessments (medical history and physical examination) will be performed on a 3 monthly basis during the first 2 years, followed by 6 monthly assessments for years 3, 4 and 5 and annually thereafter. All patients (except those with bilateral mastectomy) will have mammogram / breast MRI annually for 10 years beginning 6 months after randomisation. Radiological examinations in male breast cancer patients will be replaced by clinical examination and local chest wall ultrasound as required. Evidence of disease recurrence or new primary cancer will require histopathological and/or radiological confirmation (please refer to section 3.1 for further details).

All randomised patients will have clinical assessment visits for 10 years following their randomisation into the study. Once a patient completes 10 years of clinical assessment they will enter the survival follow up phase of the trial which will continue until 10 years after the last patient is randomised. No clinic visits will be required during the survival contact phase; information will be collected via telephone, medical records and death registries.

During the 10 year follow up patients will be assessed for local recurrence, distant recurrence (including subsequent sites of recurrence) and all new cancers (including new primary breast cancer), Information on subsequent anti-cancer treatments (PARP inhibitors and platinum salts) will also be collected as well as vital status.

During the survival phase, information (where available) on further subsequent therapies, sites of metastases and any other new cancers will be collected in addition to vital status.

Disease recurrence or new cancers should be reported on the clinical database as soon as possible after they are discovered. This includes events diagnosed during study visits but also any event diagnosed during non-study visits.

Once known, death information should also be recorded on the database as soon as possible.

Target patient population

The patient population eligible for the trial will be germline *BRCA* mutated patients with HER2 negative primary breast cancer at high risk of recurrence who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.

Triple Negative Breast Cancer (TNBC)

The following two high risk groups of TNBC patients will be included in the trial:

- Post adjuvant treatment: TNBC patients with either axillary node positive disease (any tumour size) or axillary node negative disease with primary tumour > 2cm, who have undergone surgery (breast conserving or mastectomy and sentinel node biopsy or axillary node dissection) and have completed at least 6 cycles of adjuvant chemotherapy containing anthracyclines or taxanes or the combination of both. Adjuvant radiotherapy if indicated should be completed prior to randomisation

- Post neoadjuvant treatment: TNBC patients who did not achieve complete pathological response (non pCR) following at least 6 cycles of neoadjuvant chemotherapy containing anthracyclines or taxanes or the combination of both, followed by surgery. Adjuvant radiotherapy if indicated should be completed prior to randomisation. All chemotherapy should be delivered prior to surgery. No further cycles of chemotherapy post surgery are allowed

Pathologic complete response (pCR) is defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic therapy (ie, ypT0 ypN0 /AJCC staging system). The presence of residual ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) in the surgical specimen is not excluded in the proposed definition of pCR as per FDA proposed definition. (FDA Guidance for Industry 2012).

Hormone Receptor Positive/HER2 negative Breast Cancer.

It is anticipated that patients with germline *BRCA* mutations and high risk ER/PgR positive and *HER2* negative breast cancer (including tumour grade III and axillary node positive disease) will similarly benefit from adjuvant olaparib treatment following completion of their loco-regional and chemotherapy anticancer treatment. Since the standard of care in those patients following completion of chemotherapy is adjuvant endocrine treatment, in order to combine olaparib with endocrine treatment, a potentially adverse pharmacokinetic (PK) and pharmacodynamic (PD) interaction has to be ruled out. These investigations are currently underway and provided results adequately support proceeding with evaluation of such a combination, it is anticipated that the protocol will be amended to allow inclusion of patients with *gBRCA* mutations and high-risk ER/PgR positive/HER2 negative cancers into the study. Until then, only high risk triple-negative breast cancer patients with *gBRCA* mutations will be eligible for the trial

Investigational product, dosage and mode of administration

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib and matching placebo to the investigator as green film-coated tablets.

Patients will be administered olaparib or matching placebo orally twice daily (b.i.d) at 300 mg for 12 months. Two (2) x 150 mg olaparib or matching placebo tablets should be taken at the same times each morning and evening of each day, approximately 12 hours apart with approximately 240 mL of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib/placebo tablets can be taken with a light snack (e.g. two toasts or two biscuits)

Comparator, dosage and mode of administration

Placebo will be available as green film-coated tablets matching the olaparib tablets. The placebo tablets are for oral administration and should be taken as per instructions for olaparib tablets.

Duration of treatment

Patients will be randomised in a 1:1 ratio to one of the following treatments:

- 12 months treatment with olaparib tablets po. 300 mg twice daily
- 12 months treatment with placebo tablets po. twice daily

Stratification

Patients will be stratified at randomisation by the following baseline factors:

- Prior neoadjuvant versus adjuvant chemotherapy
- Prior platinum therapy for current breast cancer: Yes/No

Within this study, patients will not be provided olaparib post discontinuation of study treatment. Patients and investigators will not be routinely unblinded to study treatment prior to the final overall survival (OS) analysis.

Outcome variable(s):

- Primary outcome variable
  - Invasive Disease Free Survival (IDFS)
- Secondary outcome variables
  - Overall Survival (OS)
  - Distant Disease Free Survival (DDFS)
  - New primary invasive breast cancer and/or epithelial ovarian cancer in patients at risk for these events
  - FACIT-fatigue symptom scale and EORTC-QLQ-C30 HrQoL scale
  - IDFS, DDFS and OS based on patients with *gBRCA* mutations confirmed by the central test (only required if population differs from the ITT (intention to treat) population)
- Safety outcome variables

- Adverse Events (AE), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology

- Exploratory outcome variables
  - Potential retrospective biomarker (mandatory) & pharmacogenetic research (optional)
  - Adjusted overall survival estimates (if applicable)

Statistical methods

The primary endpoint of the study is IDFS and patients will be randomised 1:1 to either olaparib 300mg bid or matching placebo.

Approximately1320 patients will be randomised into the study. If the true hazard ratio (HR) for the comparison of olaparib versus placebo in terms of IDFS is 0.7 then with 330 events, the analysis of IDFS will have 90% power to demonstrate a statistically significant difference in IDFS, assuming a 2-sided 5% significance level. It is estimated the study will take approximately 4 years to complete recruitment of 1320 patients. Assuming non-uniform recruitment then the required 330 events is estimated to occur at approximately 5.5 to 6 years from the start of randomisation.

An interim analysis for superiority will be performed once a minimum of 165 IDFS events have been observed from the first 660 patients recruited. It is estimated that this analysis will occur approximately 4.5 years after the first patient is randomised. It is anticipated that patient recruitment will have been completed and > 50% will have completed 12 months of study treatment. At this time both the ITT population (primary) and the population including only the first 660 patients randomised (referred to as a mature cohort, considered supportive of the ITT) will be analysed. The timing of the interim analysis and the inclusion of the mature cohort population is to give assurance that any observed treatment effect is maintained with longer term follow up (ie to reduce risk of falsely declaring the trial positive on early data). Consideration of futility will also be made at the time of interim analysis.

IDFS will be analysed using a stratified log rank test based on the study stratification factors. The HR (hazard ratio) (olaparib vs. placebo) together with its corresponding 95% confidence interval (CI) and p-value will be presented (a HR less than 1 will favour olaparib). In addition a confidence interval will be presented for IDFS corresponding to the significance level applied to the IDFS analysis based on the multiple testing procedure (MTP) defined in the protocol.

A Kaplan-Meier (KM) plot of IDFS will be presented by treatment group. The estimated 3 year IDFS rates will be summarised (using the KM curve) and presented by treatment group. Subgroup analyses will be conducted to assess consistency of treatment effect across potential or expected prognostic factors.

Secondary endpoints of OS and DDFS will be analysed at the time of the IDFS analysis as per the MTP outlined in the protocol and will use the same methodology and model as described above for IDFS. Further analyses of OS and DDFS post the final data cut off (DCO) date for IDFS may be

required for which some alpha will be reserved for formal testing. The final OS analysis will occur once data collection is complete for all patients

Exploratory analyses of OS which attempt to adjust for any potential confounding impact of subsequent use of PARP inhibitors on the control arm may be performed if an appropriate proportion of patients on the control arm receive such treatments and sufficient information is collected on subsequent therapy use. Methods such as Rank Preserving Structural Failure Time (RPSFT) (Robins et al 1991), and other methods in development will be explored. The decision to adjust and final choice of methods will be based on a blinded review of the data and the plausibility of the underlying assumptions. Other subsequent therapies may also be considered such as platinum therapies if important imbalances are reported across the treatment arms. Details will be pre-specified in the SAP (statistical analysis plan) or Payer Analysis Plan as this analysis is intended to support reimbursement appraisals.

Safety data will be summarised descriptively in terms of AEs, vital signs, clinical chemistry & haematology and physical exam and will include all patients who received at least one dose of olaparib or placebo. .

Patient reported outcomes and health related quality of life (HRQoL) will be assessed through the planned correlative study using the FACIT fatigue symptom scale and the EORTC QLQ-C30 scale (see protocol for more details).

Summaries of exploratory biomarker outcome variables and data listings will be produced and compared across the two treatment arms. Graphical methods will be widely used in exploring the characteristics and relationships of outcome variables.

An analysis of IDFS, DDFS and OS will be conducted based on patients with *gBRCA* mutations confirmed by the central test, if this population differs from the primary ITT population.

Full details of all the statistical analyses will be documented in the SAP prior to first subject in (FSI).