A PHASE 2, NON-RANDOMIZED, OPEN LABEL, SINGLE ARM, MULTI-CENTER STUDY OF TALAZOPARIB FOR NEOADJUVANT TREATMENT OF GERMLINE BRCA1/2 MUTATION PATIENTS WITH EARLY HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 NEGATIVE BREAST CANCER

Investigational Product Number:	**PF-06944076**
Investigational Product Name:	**Talazoparib**
United States (US) Investigational New Drug (IND) Number:	CCI
Protocol Number:	**C3441020**
Phase:	**2b**

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	20-December-2017	Not applicable (N/A)
Amendment 1	12-February-2018	Added clarification to the Schedule of Activities to footnotes q-u, Radiologic Assessments. Removed inflammatory breast carcinoma (IBC) patients from Section 4.1. (Inclusion Criteria) and added them to Section 4.2. (Exclusion Criteria) in response to the following feedback from the FDA: "Revise the eligibility criteria such that patients with IBC are NOT eligible. Patients with IBC should receive neoadjuvant therapy with an anthracycline and taxane combination." Removed paragraphs from Section 8.1, which referred to an external endpoint adjudication committee; this study will not require one. Header 8.4. Changed to Special Situations per CT-02 Template. Added wording: This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).
Amendment 2	27-February-2018	Added to the Schedule of Activities, footnote f, and Section 7.9.2, Physical Examinations: A clinical exam of breast and axilla should be included in each physical exam. If the patient has evidence of clinical disease progression, treatment on study should be discontinued. These patients should either switch to alternate systemic

		therapy or go straight to surgery so as not to preclude potentially curative surgery. Added to Protocol Summary (Study Design), Section 9.1 (Sample Size Determination) and Section 9.7, (Interim Analysis): If at interim analysis, 7 patients or less achieve pCR among the first 28 patients in the evaluable population, the study may be stopped for futility. Removed text pertaining to medical devices from Section 8.2.3 (Serious Adverse Events), and 8.5.1 (Medication Errors), since it is not applicable to this study. Removed from Protocol Summary (Study Design), and Section 9.7 (Interim Analysis): Predefined IA futility criteria are not binding and the totality of evidence (efficacy and safety) will be considered. Removed from Section 9.7 (Interim Analysis): However, enrollment in the study will not be interrupted for the assessment of futility at the interim analysis, as the futility boundary is not binding.
Amendment 3	16-November-2018	Throughout: minor editorial edits have been made to enhance the readability of the protocol. Throughout: term “fresh” updated to more correct term of “new at screening”. Introduction: updated latest version of Talazoparib IB to August 2018. Introduction, Protocol Summary (Background and Rationale), and Section 1.4 (Rationale for Study): added

		two references regarding talazoparib's enhancement of the cytotoxic effects of chemotherapy. Protocol Summary (Background and Rationale): Added safety data for AEs and pCR for TNBC cohort. Protocol Summary (Background and Rationale), Section 1.3.1, and Section 1.4 updated with current ASCO data and 2018 NEJM publication reference. Protocol Summary (Primary Endpoint), Table 2 (Summary of Objectives and Endpoints), Section 1.2.5 (pCR as an Endpoint in NeoAdjuvant Trials), and Section 9.3.3 (pCR in breast by Independent Central Review and Investigator); definition of pCR amended as follows (text added in bold, text removed in italics): pCR by ICR after completion of 24 weeks of neoadjuvant talazoparib followed by surgery defined as ypT0/**Tis** ypN0 (the absence of residual invasive *and in situ* cancer **in the breast and the axillary lymph nodes** on evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy). CCI [redacted] Protocol Summary (Statistical Methods): and Section 9: clarified definition of analysis populations. Protocol Summary (Study Schemata, Figure 1): updated tumor size from

		>1.5 cm to ≥T1. SOA (Table 1) and Section 7.1 (Pregnancy Testing) clarified as pregnancy testing being performed by a serum or urine test. SOA footnote q: the second sentence, "Perform post-baseline assessments every 4 weeks through Week 25, or locally determined disease progression, whichever is earlier; and at end of treatment when study results are determined" was removed. SOA footnote u: Added clarification that USS have a window of ±3 days. Section 1.2.2 updated for FDA approval of olaparib. Section 1.3 updated with latest Development Safety Update Report information. Section 1.3.1 updated with most current IB information for PRP-001 and ABRAZO studies. Section 3 updated to clarify that biopsy can be performed using institutional procedures such as dual blue dye or radioisotope tracers (since not all the sites use both methods). Section 4.1 (Inclusion Criteria), Item 2 updated to specify that patients must be willing **and able** to provide informed consent. Also, Item 6 updated (tumor size changed from >1.5 cm to ≥T1). Sections 4.1, 4.2, and 4.3.1 (Inclusion Criteria, Exclusion Criteria, and Contraception, respectively): contraception requirements updated to 7 months after the last dose of talazoparib for females and 4 months

		after the last dose of talazoparib for males (August 2018 Talazoparib IB). Section 5.4.1, Table 4 updated to include language for dose reduction and discontinuation. Section 5.5 (Investigational Product Storage) renamed Investigational Product Storage and Handling; handling instructions were added. Section 7.1 (Pregnancy Testing) corrected to at screening, and on Day 1 of Cycles 1-6 and as per the SOA. Section 8.2.3 (Serious Adverse Events) updated to clarify that Secondary Primary Malignancies should be reported as SAEs. Section 8.5.1 (Medication Errors) updated to be in line with Pfizer procceses. Subsection 8.5.2 (Overdose) added to Section 8.5 (Medication Errors and Lack of Efficacy) to incorporate language consistent with updated IB regarding overdose management (August 2018 Talazoparib IB). CCI [redacted]
Amendment 4	14-Aug--2019	Throughout document: + and – replaced with positive and negative, respectively, for clarity. Title page: Study title updated (triple negative breast cancer changed to human epidermal growth factor receptor 2 negative breast cancer). Wording also updated in Protocol Summary and Section 3, Study Design and elsewhere

		in the protocol as appropriate. Summary (Background and Rationale): Added wording and references 1-4 and 8-9 for further background information on breast cancer. Renumbered references accordingly. Schedule of Activities: removed need for urinalysis at 'post surgical follow up' visit. Section 1.2.5 (Neoadjuvant Therapy for ER positive Germline Breast Cancer Susceptibility Gene Positive Breast Cancer) added to provide background information on germline BRCA 1/2 mutations in HR positive breast cancer. Section 3 (Study Design): Patient numbers and study design updated to address lower than expected enrollment. Section 4.1 (Inclusion Criteria): • Criterion #1 updated to indicate that testing for gBRCA mutations may be performed at a local laboratory. Updated language in the Protocol Summary (Study Design), SoA (Footnote ee), and Section 3 (Study Design) accordingly. This change was made to allow more flexibility for enrollment. • Criterion #5 updated to remove the requirement for patients to have triple negative invasive breast cancer. Patients with hormone receptor positive disease will be permitted. This change was made to allow more flexibility in enrollment. • Criterion #6 updated to Tumor ≥ T1, **N0-3**.

		• Criterion #11 updated for methods of contraception; changed from 2 highly effective methods to 1 highly effective method, as per the August 2018 Talazoparib IB. Section 4.2 (Exclusion Criteria): • Criterion #7: modified language in first bullet to allow patients to enter the study if they have stage 1 melanoma which does not require any further treatment after adequate surgical excision. This change was made to allow more flexibility for enrollment. • Criterion #1 updated for methods of contraception; changed from 2 adequate methods to 1 highly effective method (highly effective methods are detailed in Section 4.3.1), as per the August 2018 Talazoparib IB. Section 4.1, Inclusion Criteria: Criteria adjusted clarify that both early and locally advanced disease are permitted. Section 4.3.1, Contraception: language updated for methods of contraception; changed from 2 highly effective methods to 1 highly effective method, as per the August 2018 Talazoparib IB. Section 4.3.2 (Women of Childbearing Potential) added to align with the updated Pfizer protocol template. Section 6.1.1 (Screening for gBRCA Mutations) added to capture changes in Inclusion Criteria #1 for gBRCA screening requirements. Section 9.1, Sample Size Determination: Background information added for HR

		positive breast cancer. Section 9.1, Sample Size Determination: wording updated to reflect a reduction in sample size for the study. Updated language in the Protocol Summary (Study Design), Section 3 (Study Design), and Section 9.9 (Interim Analysis) accordingly. This change was made due to unexpected low enrollment rates. Section 7.9.4: added Urinalysis column and tests to Table 7. CCI [redacted] Section 9.9, Interim Analysis: Wording updated to reflect a reduction in sample size for the study. References: References added and reference numbers added/linked to relevant sections (Summary, Sections 1.25 and 9.1. Other references were re-numbered accordingly.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Overview

Talazoparib (also known as PF-06944076, MDV3800, BMN 673) is being investigated for the treatment of germline breast cancer susceptibility gene 1/2, (gBRCA1/2), mutation-positive, human epidermal growth factor receptor 2 (HER2) negative breast cancer.

Background and Rationale

Breast cancer is a biologically diverse and genetically heterogeneous disease.[1,2] Breast cancer susceptibility gene 1(BRCA1) and breast cancer susceptibility gene 2 (BRCA2) are key components in the repair pathway for deoxyribose nucleic acid (DNA) double strand breaks,[3] and mutations in these genes account for 20% to 25% of hereditary breast cancers and 5% of all breast cancers.[4] A substantial portion of patients with gBRCA mutated breast cancer have hormone receptor-positive disease, including 20 30% of gBRCA1 carriers and 45 72% of gBRCA2 carriers.[5]

Approximately 15% of all breast cancers are triple negative. They can be defined by the lack of estrogen, progesterone, and HER2 receptors. They are more commonly associated with younger women, pre-menopausal women of African American race and BRCA1 mutation carriers. Triple-negative breast cancers (TNBCs) are generally more aggressive in nature and associated with visceral and soft tissue disease. The incidence of BRCA 1 and 2 mutations in patients with TNBC has been reported to be between 9.6 to 10.6%.[6,7] In a study of 469 TNBC patients, gBRCA1/2 mutation prevalence was also shown to vary by race: Ashkenazi Jewish (50 %), Caucasian (33.3 %), Asian (28.5 %), African Americans (20.4 %), and Hispanic (20 %). The prevalence of genetic mutations also differed by age at diagnosis, with most patients <40 years (43.8 %) of age. Various studies have demonstrated that TNBCs are associated with a poorer prognosis than luminal breast cancers. A Canadian series, including approximately 1600 triple negative cancers conducted by Dent, R et al[8] demonstrated worse long term outcomes in terms of distant recurrence and death in triple negative tumors compared to non-triple negative tumors.

The standard of treatment for neoadjuvant treatment is variable, but mostly focuses on the use of anthracycline- taxane regimens. Other regimens used include adriamycin plus cyclophosphamide (AC). Cyclophosphamide methotrexate, and fluorouracil (CMF) is another option which offers less toxicity; however, it has a longer duration of therapy.

Platinum therapies have also shown efficacy in HER2 negative breast cancer, in particular germline breast cancer susceptibility gene (gBRCA) mutant tumors, as these tumors have defects in homologous recombination (hR), rendering them more susceptible to deoxyribose nucleic acid (DNA) cross linking agents such as platinums. Retrospective neoadjuvant subject series have suggested that primary breast cancer in BRCA1 carriers is platinum-sensitive and relatively unresponsive to anthracyclines and/or taxanes[9] while other studies have found that BRCA1 is relatively responsive to anthracyclines and/or taxanes while BRCA2 disease is less responsive than sporadic primary breast cancer to these drug classes.[10]

The GeparSixto (NCT01426880) and CALGB (NCT00632853) trials examined the efficacy of adding platinum to neoadjuvant regimens in triple negative breast cancer. In GeparSixto, the pathological complete response (pCR) rates (breast/axilla) increased from 36.9% to 53.2%; in the BRCA subgroup, an increase in pCR by 25% (probability value [*p*]=0.008) was observed. The CALGB/Alliance trial showed an increase in pCR with the addition of carboplatin for breast/axilla (54% vs 41%; *p*=0.0029). Since these studies were underpowered for long term outcome, it is difficult to assess long term benefit. Therefore, the role for platinum therapy in TNBC still remains unclear and warrants further investigation in larger trials with examination of long term outcomes. There have been studies resulting in improved disease-free survival (DFS) in patients who achieved pCR with platinum agents and BRCA mutation. Frasci et al[11] reported that in TNBC patients treated with eight cisplatin-epirubicin-paclitaxel weekly cycles, 62% showed pCR in both breast and axilla, and the projected 5-year DFS was 90% and 56% in pCRs and non-pCRs, respectively.

The BRCA1 gene is expressed in several tissues, such as breast and ovarian tissue. Currently, more than 1600 mutations have been identified in the BRCA1 gene, and the majority of them promote frameshifts resulting in missense or non-functional protein. Women with BRCA1 mutations have an increased risk of developing breast and ovarian cancer, while men have a higher risk, to a lesser extent, of developing prostate cancer.[12]

BRCA2 does not share a high degree of sequence homology with other known genes, and the generated protein is comprised of regions with domains that are undefined.[13] Currently, more than 1800 mutations have been identified in BRCA2, that include frameshift deletions, insertions, or nonsense mutations that lead to premature truncation of proteins.

It has been demonstrated that BRCA1 and BRCA2 tumor suppressor genes perform a critical role in the response to cellular damage through activation of specific DNA repair processes and play an important part in DNA repair and as transcriptional regulators.[14]

Inhibition of poly (ADP-ribose) polymerase (PARP) catalytic activity contributes to the process of synthetic lethality-defined as a combination of two DNA repair pathway defects which may be lethal to the cell-resulting in single-strand breaks that require homologous recombination DNA repair for survival. PARP inhibitors (PARPi) induce synthetic lethality in tumor cells containing mutations and/or deletions in genes involved in homologous replication or other DNA pathways, including BRCA1 and BRCA2.

Clinical trials have shown that PARPi are beneficial in the treatment of patients with breast cancer that are carriers of germline BRCA mutations. In a phase 1 trial, olaparib (NCT00516373; 10 to 600 mg twice a day) treatment of solid tumors of patients with breast cancer with no gBRCA mutations vs. patients with breast cancer with gBRCA mutations, resulted in an objective response rate (ORR) of 15% and 33%, respectively[15] in a phase 2 trial (NCT00494234) of single-agent olaparib in patients with breast cancer with BRCA1/2 mutation and advanced disease, investigated two dose levels (cohort 1: 400 mg twice daily [bd] and cohort 2: 100 mg bd) and demonstrated an ORR of 42% and 25%, respectively. Progression-free survival (PFS) was 5.7 and 3.8 months for cohorts 1 and 2, respectively. A phase I study of niraparib (NCT00749502; 30 to 400 mg once a day) for treatment of solid

tumors resulted in an ORR of 40% in patients with gBRCA mutations vs. 18% in the general breast cancer population.[16] Lastly, a first-in-human trial of oral talazoparib (NCT01286987; 25 to1100 ug/day) resulted in an ORR of 65% and 33% in solid tumors of gBRCA patients with ovarian or breast cancer, respectively.[17]

Talazoparib is a potent, orally bioavailable, small molecule PARPi in development for the treatment of a variety of human cancers. Single agent talazoparib treatment demonstrates potent antitumor effects in tissue culture studies, mouse tumor xenograft models, and in Phase 1 studies in patients with solid tumors. Talazoparib has also been shown to enhance the cytotoxic effects of DNA damaging chemotherapy.[18,19]

Despite advances in the understanding of the biology of gBRCA associated TNBC, treatment options remain limited. PARPi, as well as platinum-based combination therapies, have emerged as regimens of potential interest and in particular, therapy with single agent PARPi could present significant advantages over chemotherapy regimens through potentially improved tolerability.

The PARP inhibitor olaparib, which was first approved by the Food and Drug Adminstration (FDA) in 2014 for patients with advanced ovarian cancer with gBRCA mutations, was assessed during a Phase 3 study (OlympiAD; NCT02000622) in metastatic gBRCA mutated breast cancer. This trial included patients with HER2 negative, metastatic breast cancer that were either hormone receptor (HR) positive or triple negative; a subgroup of the patient population (approximately 50%) were defined as TNBC. PFS was 7 months in the olaparib group vs. 4.2 months in the chemotherapy group (observed hazard ratio=0.58; 95% CI, 0.43 to 0.80; p=0.009). The objective response rate was 59.9% in the olaparib arm vs. 28.8% in the chemotherapy arm. Olaparib was determined to be effective against triple-negative breast cancers that arise in women with inherited, germline BRCA mutations (observed hazard ratio in the TNBC subgroup=0.43).[20]

The Phase 2 ABRAZO study, presented at ASCO 2017, demonstrated clinical activity of single agent talazoparib in advanced triple negative, gBRCA mutant breast cancer. ABRAZO (673-201; NCT02034916) is an open-label Phase 2, single arm study investigating the clinical efficacy and safety of single-agent talazoparib in 83 heavily pre-treated patients with gBRCA positive advanced breast cancer. The primary endpoint was ORR by independent radiology review. Cohort 1 consisted of 49 patients who previously responded to platinum-based chemotherapy and subsequently developed disease progression. A 21% ORR (95% confidence interval [CI]: 10 to 35) was observed in this group of patients. Cohort 2 consisted of 35 patients who developed disease progression following at least three lines of non-platinum-based therapy. This group of patients had a 37% ORR (95% CI: 22 to 55).

Another study in the advanced breast cancer setting conducted by Litton et al. was recently published in the New England Journal of Medicine.[21,22] This study (EMBRACA, NCT01945775) was a randomized, open-label, Phase 3 trial in which patients with advanced breast cancer and a germline BRCA1/2 mutation were assigned, in a 2:1 ratio, to receive talazoparib (1 mg once daily) or standard single-agent therapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine in continuous 21-day cycles). The primary endpoint was progression-free survival. Of the 431 patients who underwent randomization, 287 were assigned to receive talazoparib and 144 were assigned to receive standard therapy. Progression-free survival was significantly longer in the talazoparib group than in the standard-therapy group (hazard ratio for disease progression or death, 0.54; 95% CI, 0.41 to 0.71; p<0.001; medians 8.6 months vs. 5.6 months). The hazard ratio for overall survival based on interim analysis at the time of the final progression-free survival analysis was 0.76 (95% CI, 0.55 to 1.06; p=0.11 [57% of projected events]; medians 22.3 months vs. 19.5 months). The objective response rate was higher in the talazoparib group than in the standard-therapy group (62.6% vs. 27.2%; odds ratio, 5.0; 95% CI, 2.9 to 8.8; p<0.001). In all clinically-relevant subgroups, a consistent PFS benefit in favor of talazoparib was observed in comparison with physician's choice of treatment (PCT), regardless of hormone-receptor status (hormone receptor positive [HR positive]: hazard ratio 0.47, 95% CI, 0.32 to 0.70; or TNBC: hazard ratio 0.60, 95% CI, 0.41 to 0.87) BRCA mutation subtype, history of central nervous system (CNS) metastasis, visceral/non-visceral disease, or number of prior cytotoxic chemotherapies for advanced disease. Complete response was seen in 5.5% of patients with talazoparib therapy vs zero patients receiving PCT and partial response was seen in 57.1% vs 27.2%, respectively. In an exploratory analysis, time to end of first post-study therapy was longer with talzapari (hazard ratio 0.68; 95% CI; 0.51 to 0.91). Talazoparib was approved in October 2018 by the US FDA for the treatment of adult patients with deleterious or suspected deleterious germline BRCA- mutated (gBRCAm), HER2 negative locally advanced or metastatic breast cancer.

Talazoparib was generally well tolerated, and few adverse events (excluding progressive disease) led to permanent treatment discontinuation (5.9% in talazoparib arm vs 8.7% in PCT). Most non-hematologic toxicities were lower-grade, and the more common hematologic toxicities were managed by dose interruption or dose reduction and supportive care as needed.

An investigator-initiated research (IIR) study at MD Anderson Cancer Center titled "Neoadjuvant Talazoparib for Patients With a BRCA Deleterious Mutation" explored the feasibility of neoadjuvant talazoparib in a two part study (NCT02282345). Part 1, which evaluated a lead-in of 2 months of talazoparib single agent followed by standard chemotherapy and surgery, is complete and was accepted for publication in NPJ Breast Cancer.[23] Decreases in tumor volume (as assessed by the investigator) occurred in 13 out of 13 patients following 2 months of talazoparib monotherapy (1 mg). The median tumor volume decrease after two months of treatment with talazoparib was 88% (range of 30 to 98%). Notably, all TNBC patients achieved either residual cancer burden (RCB)-0 or RCB-1 following completion of the protocol assigned therapy and surgery. In this pilot study, talazoparib was well tolerated with no Grade 4 or 5 toxicities observed, and only one patient required dose reduction due to Grade 3 neutropenia. Following these data on efficacy and

tolerability, part 2 of the study was opened and evaluated 24 weeks of talazoparib monotherapy followed by surgery with no additional chemotherapy. This part of the study enrolled 20 patients total, who received talazoparib monotherapy for 6 months followed by surgery and assessment of pCR. All patients were BRCA positive and the majority was stage 2 or 3; most patients had triple negative breast cancer. pCR to single agent talazoparib was 10/19 = 53%, (95% CI = 32%, 73%). Residual Cancer Burden was also evaluated: RCB 0 (no RCB) + RCB 1 (minimal residual disease) was 12/19 = 63**%**, 95% CI = 41%, 81%. There were 14 patients in the TNBC cohort. Of those patients, 7 (50%) patients had RCB-0, 1 (7.4%) patient had RCB-1, 4 (28.5%) patients had RCB-2 and 2 (14.2%) patients had RCB-3. Therefore, the pCR rate was 50% and pCR +RCB-1 was 57.1%. Of note, pCR occurred in both metaplastic carcinoma and lobular carcinoma. Talazoparib was well tolerated with acceptable adherence and manageable toxicities.

In terms of hematologic toxicities, 8 of 20 (40%) patients had Grade 3 anemia. There were no patients with Grade 4 anemia. There was one case of Grade 4 thrombocytopenia. Neutropenia occurred in 4 patients at Grade 2 (20%) and Grade 3 in 3 (15%) patients.

For non-hematologic toxicities, most were Grade 1 and 2. The most common toxicities occurring in >50% of patients were nausea, fatigue, and alopecia. Nineteen (19) of 20 patients completed 6 months of therapy; one patient completed 5 months and then received chemotherapy prior to surgery. Two patients had dose reductions to 0.75 mg, 6 patients reduced to 0.5 mg, and one patient had a dose reduction to 0.25 mg. All dose reductions were due to hematologic toxicities.

The findings from this study demonstrate promising efficacy for talazoparib in the neo-adjuvant gBRCA positive early breast cancer setting. Talazoparib is the first single targeted therapy to achieve pCR in BRCA positive patients, including TNBC. This study warrants the larger confirmatory trial (C3441020).

The present study is a non-randomized, Phase 2 study in gBRCA1/2 positive early HER2 negative breast cancer, which will evaluate the safety and efficacy of talazoparib in the neoadjuvant setting. It will also evaluate patient reported outcomes CCI [redacted] in this patient population.

Objectives and Endpoints

Primary Objective

- To evaluate the pCR to talazoparib after 24 weeks of neoadjuvant talazoparib therapy followed by surgery. pCR (breast and axilla) will be assessed by independent central review (ICR).

Secondary Objectives

- To evaluate pCR (breast and axilla) by investigator.

- pCR in breast only (by ICR).
- Residual cancer burden by ICR.
- To evaluate long term outcome by assessment of 3-year EFS (event free survival) and overall survival (OS).
- To evaluate the safety and tolerability of talazoparib.
- To describe the steady-state pharmacokinetics (PK) of talazoparib in patients with gBRCA mutation-positive, HER2 negative breast cancer.
- To evaluate the following patient-reported outcomes (PRO):
  - Global health status/Quality of Life (QoL), functioning, and symptoms (including nausea and vomiting);
  - Missed expected menstrual period; this objective captures the concept of fertility preservation through PRO, since there is a possible fertility sparing effect of talazoparib versus chemotherapy.

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Primary Endpoint

- pCR by ICR after completion of 24 weeks of neoadjuvant talazoparib followed by surgery defined as ypT0/Tis ypN0 (the absence of residual invasive cancer in the breast and the axillary lymph nodes on evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy).

Secondary Endpoints

- pCR by investigator.
- RCB by ICR.
- pCR (in breast) by ICR.
- EFS (estimated at 3 years).
- OS (estimated at 3 years).
- Type, incidence, severity (as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v4.03), seriousness and relationship of study medications to adverse events (AE) and any laboratory abnormalities.
- Time to definitive deterioration in global health status/QoL per EORTC (European Organisation for Research and Treatment of Cancer) QLQ (Quality of Life Questionnaire)-C30.
- Time to definitive deterioration in nausea and vomiting symptoms per EORTC QLQ-C30.
- Change from baseline in global health status/QoL, functioning, and symptoms per EORTC QLQ-C30 and EORTC QLQ BR-23.
- Proportion of patients with deterioration, improvement and no change in nausea and vomiting symptoms.
- Change from baseline in proportion of patients with missed expected menstrual period per PRO-CTCAE**.**
- PK of talazoparib using sparse sampling (trough concentrations [C_{trough}] at limited timepoints).

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- [redacted]

[redacted]

Study Design

This is a non-randomized, Phase 2, single-arm, open-label, multi-center study enrolling patients with gBRCA1/2 HER2 negative breast cancer. Approximately sixty patients will be enrolled in the study and treated with talazoparib 1 mg once daily (QD) for 24 weeks followed by surgery. With a sample size of 60 patients, the two-sided 80% exact Blaker confidence interval (CI) for the pCR rate would be at most 17% wide. If a pCR=50% is observed, the lower bound of the exact 80% CI would exclude 41%.

An interim futility analysis, designed based on Bayesian predictive probability (PP), will be conducted once 28 evaluable patients are assessed for pCR. The PP is the probability of concluding a positive result by the end of the trial based on the cumulative information in the current stage. The trial will be considered a success if the posterior probability that the true pCR rate exceeds 45% is ≥80%. Predictive probability <10% was set as the futility boundary and assumed a non-informative beta (1,1) prior. Once 28 evaluable patients are assessed for pCR, if 11 responses or less are observed, the predictive probability of the trial being successful at the full sample size is less than 10%, at which point the Sponsor would recommend stopping the study due to futility. If ≥12 responses are observed in the first 28 evaluable patients, the study will continue enrolling to 60 evaluable patients.

The evaluable population is the primary analysis population at the interim and final analysis. Patients that do not complete talazoparib treatment for 24 weeks, do not have surgery, or for whom the ICR assessment of the post surgery specimen is not available, will be excluded from the evaluable population (unless they progressed or died before pCR could be assessed). Patients who die or progress before pCR could be assessed will be included as non-responders in the analyses. The intent-to-treat (ITT) population will include all patients who received at least 1 dose of talazoparib, regardless of whether or not they are considered evaluable.

A patient will participate in up to 4 periods: screening, talazoparib treatment phase, safety follow-up, and long-term follow-up. Patients will be evaluated at screening for the presence of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation as confirmed by a local Clincal Laboratory Improvement Amendments (CLIA) certified test. Patients must also consent to a blood sample for central genomic assessment using the BRACAnalysis Companion Diagnostics (CDx) test by Myriad Genetics, except for patients who already have evidence of BRCA1/2 mutation by MYRIAD BRCAnalysisCDx post 2016. Long-term follow up period is at least 5 years, which starts from the date of surgery for EFS and after first dose of drug for OS. Figure 1 provides a study schematic.

Safety follow-up (end of treatment visit) will occur 28 days after the last dose of study drug or before initiation of a new antineoplastic or investigational therapy, whichever occurs first. There will also be an additional post- surgical safety follow up, 4 weeks after surgery for assessment of wound healing. Long term follow-up will begin after date of surgery for EFS and OS after first dose of talazoparib.

Study Treatments

Patients will receive talazoparib 1 mg daily for 24 weeks, followed by breast surgery, which should occur within 4 to 6 weeks (no longer than 6 weeks) of the last dose. If hematological toxicity is present (ie, neutropenia/thrombocytopenia), the investigator will decide whether surgery will proceed according to schedule; a washout period is not needed.

Statistical Methods

Analysis populations:

Evaluable population is defined as all patients enrolled in the study who receive 24 weeks of talazoparib treatment 1 mg once daily (QD), undergo breast surgery and pCR assessment, as well as those patients who progress or die before pCR can be assessed. The evaluable population is the primary analysis population for all efficacy endpoints at the interim analysis as well as the final analysis. Patients who progress or die before pCR can be assessed (regardless of whether or not they received 80% of study treatment) by investigator and by ICR will be considered as non-responders in the evaluable population. If a patient receives less than 80% of the protocol required treatment, undergoes surgery and achieves pCR by ICR, the patient will be counted as a responder in the ITT population, but will not be included in the evaluable population.

The intent to treat (ITT) analysis population is defined as all patients enrolled in the study who received at least one dose of talazoparib. All efficacy analyses will also be reported in the ITT analysis population. The safety population is defined as all patients enrolled in the study who received at least one dose of talazoparib (which is the same as the ITT population in this study). All safety analyses will be reported using the safety population.

The PRO analysis population is defined as all patients who completed a baseline and at least one post baseline quality-of-life assessment prior to the end of study treatment.

The PK analysis population is defined as all patients treated with talazoparib for whom drug plasma concentration results (from at least 1 visit) are available. For the PK analysis population, talazoparib concentrations will be summarized descriptively by nominal time and talazoparib dose strength. Additionally, a subgroup of PK samples which meet pre-defined steady-state acceptance criteria (as detailed in the study statistical analysis plan [SAP]) will be summarized by nominal time and a within-patient average talazoparib steady state trough concentration will be listed by patient from this population.

Analysis methods

pCR rate by ICR is defined as the number and percentage of patients achieving pCR by independent central review after talazoparib treatment for 24 weeks, followed by surgery, among all patients in the evaluable population. Patients who progress or die before pCR can be assessed will be considered as non-responders. pCR rate will be evaluated at the time of the interim and final analyses and will be summarized along with the exact 80% and 95% CI. pCR by ICR will also be summarized in the ITT population, along with the exact 80% and 95% CI. Patients who discontinue treatment or the study prematurely, are lost to follow-up, withdraw consent, progress or die before pCR can be assessed by central review will be considered as non-responders in the ITT population analysis.

pCR rate by investigator is defined as the number and percentage of patients achieving pCR by investigator review after talazoparib treatment for 24 weeks, followed by surgery, among all patients in the evaluable population. pCR rate by investigator will be evaluated at the time of the interim and final analyses and will be summarized along with the exact 95% CI. pCR by investigator will also be summarized in the ITT population, along with the exact 95% CI. Patients who discontinue treatment or study prematurely, are lost to follow-up, withdraw consent, progress or die before pCR can be assessed by investigator will be considered as non-responders in the ITT population analysis.

Residual cancer burden by ICR will be reported as a categorical variable with four classes (categories) RCB 0 (pCR), I (minimal RCB), II (moderate RCB), and III (extensive RCB). Number and percentage of patients in each category will be reported along with exact 95% CI. The analysis of RCB by ICR will be conducted in the evaluable population.

pCR rate in breast by ICR is defined as the number and percentage of patients achieving pCR in breast by independent central review after talazoparib treatment for 24 weeks, followed by surgery, among all patients in the evaluable population. pCR in breast rate will be summarized using descriptive statistics along with the exact 95% CI. pCR rate in breast by ICR will also be summarized in the ITT population along with 95% CI. Patients who discontinue treatment or study prematurely, are lost to follow-up, withdraw consent, progress or die before pCR in breast can be assessed by central review will be considered as non-responders in the ITT population analysis.

EFS is defined as the time from surgery date to first documentation of local or distant recurrence, death, or initiation of antineoplastic therapy before documentation of first relapse. Patients discontinuing study before documentation of first relapse or death, but after surgery, will be censored observations for EFS. EFS at 3 years is defined as the probability of being event-free at 3 years using Kaplan Meier methods. The 95% CI for EFS at 3 years will be calculated using the Brookmeyer-Crowley method[24] EFS at 3 years will be summarized in the evaluable population.

OS is defined as the time from first dose of talazoparib to death due to any cause. Patients not known to have died at the time of the analysis will be right censored on the date they were last known to be alive before the analysis data cutoff date. Details on censoring conventions will be presented in the statistical analysis plan. OS at 3 years is defined as the probability of being alive at 3 years after first dose of talazoparib using Kaplan-Meier methods. The 95% CI for OS at 3 years will be calculated using the Brookmeyer-Crowley method. OS will be summarized in the evaluable and ITT population.

Time to definitive deterioration of patient-reported global health status/QoL (defined as ≥10-point decrease from baseline without any subsequent <10-point decrease) will be summarized using the Kaplan-Meier method and will include the median and 95% CIs.

Time to definitive deterioration of patient-reported nausea and vomiting symptoms (defined as ≥10-point increase from baseline without any subsequent <10-point increase) will be summarized using the Kaplan-Meier method and will include the median and 95% CIs.

Longitudinal mixed-effect-analyses will be used to assess over time change from baseline in nausea and vomiting symptoms, CCI [redacted] functioning, symptoms, and general health status.

The proportion of female patients with missed expected menstrual period post-baseline per Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE; vs proportion of patients with missed expected menstrual period at baseline); and proportion of patients with deterioration in nausea and vomiting symptoms (vs no deterioration) will be compared.

All safety analyses will be performed using the safety population.

Drug exposure in the safety analysis population will be summarized using descriptive statistics.

Treatment-emergent safety data will be collected from the first dose of study drug treatment through 28 days after the date of permanent discontinuation from study or before initiation of new antineoplastic or investigational therapy, whichever occurs first.

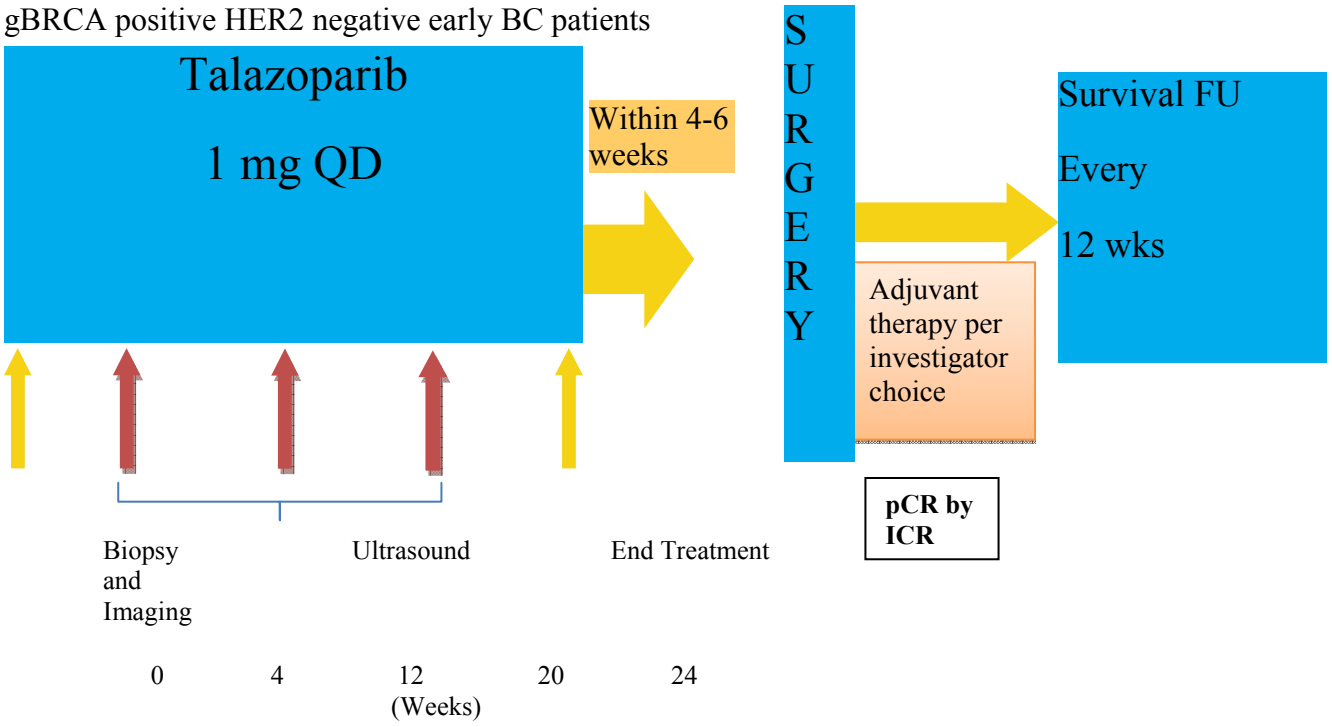
The safety of talazoparib will be evaluated by the analysis of incidence of serious and non-serious adverse events (AEs), severity of adverse events, incidence of dose modifications and of permanent treatment discontinuation due to adverse events, and incidence of new clinically significant changes in clinical laboratory values and vital signs.

Adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) and classified by severity using the CTCAE, version 4.

The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and severity. Descriptive statistics will be used.

Laboratory values will be classified by severity using the CTCAE, version 4. Laboratory shift tables of baseline to maximum post-baseline results to each subsequent visit will be produced as appropriate.

Figure 1. Study Schematic: Single Agent Talazoparib



Target Enrollment: **n=60**

Key Criteria:

- Tumor ≥ T1, N0-3;
- No evidence of distant metastasis;
- Early HER2 negative BC;
- gBRCA mutation-positive;
- No previous or concomitant anti- cancer therapies used for the treatment of cancer in the last 3 years;
- Prior surgical treatment for contralateral DCIS allowed.

Abbreviations: gBRCA= germline mutation of breast cancer susceptibility gene; HER2 = human epidermal growth factor receptor 2; BC=breast cancer; mg=milligram; QD=once a day; FU=follow-up; pCR=pathological complete response; ICR=independent central review; DCIS=ductal in situ carcinoma.

SCHEDULE OF ACTIVITIES

The schedule of activities table (Table 1) provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections (Section 6 and Section 7, respectively) of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the patient.

Table 1. Study Schedule of Activities

Visit Identifier[a]	Screening	C1D1[b]	C1D15	C2D1	C2D15	D1 of C3-C6	End of Treament Visit[c]	Surgery	Post-surgical Follow-up[dd]	Long-Term Follow-up[d]
Visit Window	**≤28 days prior to randomization**									
Informed consent,[e] SSID number	X									
Medical history (including tumor history)	X									
Eligibility Criteria	X									
Registration	X									
Physical examination (including vital signs)[f]	X	X	X	X	X	X	X			
ECOG Performance status	X	X		X		X	X			
Baseline signs and symptoms		X								
Laboratory[g]										
Hematology	X	X	X	X	X	X	X		X	
Blood chemistry	X	X	X	X	X	X	X		X	
Urinalysis	X									
Coagulation	X								X	
[redacted] CCI		[redacted]					[redacted]			
Serum or Urine Pregnancy test/contraception check	X	X		X		X	X			
CCI [redacted]	[redacted]									

Visit Identifier[a]	Screening	C1D1[b]	C1D15	C2D1	C2D15	D1 of C3-C6	End of Treament Visit[c]	Surgery	Post-surgical Follow-up[dd]	Long-Term Follow-up[d]
Visit Window	**≤28 days prior to randomization**									
CCI										
CCI										
Blood sample for PK[t]				X		X (C3 and C4 only)				
C C										
CCI										
Blood sample for BRCA status[ee]	X									
CCI										
ECG[p]	X									
Radiographic Assessments[q]										
CT/PET/MRI scan CHEST[q]	X									
CT/PET/MRI scan ABDOMEN AND PELVIS[r]	X									
Bone Scan[s]	X									
Breast imaging (Mammogram/USS/MRI)[t]	X			X (USS only)		X (USS only, C4 and C6 only)				
PRO Assessments[u]										
Antiemesis medication log[v]			X	X	X	X	X		X	
EORTC QLQ-C30[w]		X	X	X	X	X	X		X	
EORTC QLQ-BR23[w]		X	X	X	X	X	X		X	
PROCTCAE[w]		X	X	X	X	X	X		X	
CC										
Tumor Tissue Specimen (FFPE)[x]								X		
Talazoparib[y]		→	→	→	→	→	→			

Visit Identifier[a]	Screening	C1D1[b]	C1D15	C2D1	C2D15	D1 of C3-C6	End of Treament Visit[c]	Surgery	Post-surgical Follow-up[dd]	Long-Term Follow-up[d]
Visit Window	**≤28 days prior to randomization**									
Concomitant medication	X	→	→	→	→	→	→	→	→	
Serious and non-serious adverse event monitoring[z]	X	→	→	→	→	→	→	→	→	
New antineoplastic therapy[aa]										X
Local recurrence/disease progression										X
Diagnosis of myelodysplastic syndrome or acute myeloid leukemia[bb]										X
Survival status[cc]										X

Abbreviations: C=Cycle; CTC=Circulating Tumor Cells; CCI ; CT=Computed Tomography; D=Day (of study); ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FFPE=Formalin-fixed, paraffin-embedded; HRQL=health-related quality of life; HRU=healthcare resource utilization; MRI=Magnetic Resonance Imaging; PK=Pharmacokinetics; PRO=Patient reported outcomes; PROCTCAE=Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events; SSID=social security identification;USS=Ultrasound scan; CCI

a. Day relative to start of study treatment (Day 1).

b. Cycles are 4 weeks. A ± 3-day window is allowed for all study assessments, including the time between randomization and first dose. Study Day 1 is the day that the patient receives the first dose of study drug treatment. Patients must not go more than 30 days between drug dispensing visits.

c. EOT visit is usually scheduled for 28 days post last dose of study medication or after permanent treatment discontinuation or before initiation of a new antineoplastic or investigational therapy, whichever occurs first. Phone patients for adverse event follow up if they do not come to the clinic.

d. Long-term follow-up begins after safety follow-up and may be conducted by telephone every 12 weeks until the patient dies or withdraws consent for follow-up, or the study is terminated by the Sponsor.

e. Obtain any time before any study-specific procedures. Ensure consent is on the current version of the form approved by the ethics committee (EC) and Sponsor. Complete, sign, and fax or email the form with requested items to the sponsor or designee at least 2 business days before enrollment. Patient may proceed to Day 1 visit or enrollment when sponsor or designee approves by signed form or email correspondence.

f. Physical Exam: Assess systems (eg, general appearance, head, eyes, ears, nose, mouth, throat, skin, heart, lung, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal) per standard of care at the study site or as clinically indicated by symptoms. A clinical exam of breast and axilla should be included in each physical exam. If the patient has evidence of clinical disease progression, treatment on study should be discontinued. These patients should either switch to alternate systemic therapy or go straight to surgery so as not to preclude potentially curative surgery. Vital sign measurements (blood pressure, heart rate, and temperature) and weight will also be assessed. Height will also be measured at screening.

g. Patient to complete QoL questionnaires and have blood samples collected before the first dose of study drug on Day 1. If the screening test is performed >7 days before the start of treatment, repeat the test on Day 1.

[redacted]

l. Blood Sample for Pharmacokinetics: Plasma PK samples (4 mL venous blood samples collected into appropriately labeled lavender-top K_2EDTA [dipotassium ethylenediaminetetraacetic acid] tubes for talazoparib determination) will be collected pre-dose on C2D1, C3D1, and C4D1 only. Patients must be instructed to withhold their daily dose of talazoparib on PK sampling days until the pre-dose PK sample and safety assessments (ie, hematology, blood chemistry, and ECGs) have been completed. All patients: Record the dose amounts and time of dose administration on both the day of and the day before PK sampling. Record the date and time of each PK sample. For additional details, see Section 7.5 and the Study Laboratory Manual.

[redacted]

p. Single ECG, to be done locally.

q. If scans are done within 6 weeks prior to the start of the screening period (informed consent from signing date), they do not need to be repeated. Any of the imaging modalities (CT/PET/MRI) can be used.

r. Pelvis scan (CT/PET/MRI) to be done as clinically indicated.

s. Bone scan to be done as clinically indicated.

t. Breast imaging (Mammogram/USS/MRI): any one of the three imaging modalities can be used; unless indicated otherwise in the Schedule of Activities. USS have a window of ±3 days.

u. Ask the patient to complete the questionnaires before any other study activities. Questionnaires should be completed while alone in the same order at each visit.

v. An electronic patient reported-antiemesis medication log will be used to record antiemesis medication taken by the patients for 7 consecutive days prior to each clinical visit. Since there is no patient visit scheduled for Day 7, the patient will be asked to record this information at home.

w. Patient reported outcomes will be assessed electronically to evaluate global health status/QoL, functions, and symptoms using the EORTC QLQ C30 and QLQ BR23 questionnaires; [redacted] Additional patient reported outcomes will be assessed electronically to evaluate the proportion of patients with missed expected menstrual period per PRO-CTCAE.

x. Tumor tissue from the surgical specimen will be required. This should be sent to the central lab as soon as possible for evaluation of the primary endpoint (pathological complete response).

y. Drug supply must be taken into account when scheduling visits during windows. Visit procedures may be split across the window to allow for drug resupply and completion of study procedures. Instruct patient to self-administer study drug treatments. Administer talazoparib in the clinic on study days with PK assessments.

z. Collect serious and non-serious adverse event information from the time of signed informed consent through and including a minimum of 28 calendar days after the last administration of the IP. If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started.

aa. Record subsequent treatment information for patients starting a new antineoplastic or investigational therapy.

bb. Record any diagnosis of myelodysplastic syndrome or acute myeloid leukemia and report as a serious adverse event (SAE). Provide tissue samples and other supporting data used to enable the diagnosis of myelodysplastic syndrome or acute myeloid leukemia for central review if requested.

cc. Obtain survival status every 12 weeks by any means including telephone, clinic visit, chart review, or by communicating with an individual (eg, family, friend, referring health care provider) who is knowledgeable of the patient's survival status.

dd. Post-surgical follow-up: a clinical examination of the post-surgical wound should be carried out and laboratory tests as indicated should be performed.

ee. BRCA testing can be performed using a local, CLIA certified blood test. If local test is done (other than Myriad BRACAnalysisCDx post 2016), an additional sample will need to be sent for central testing to MYRIAD genetics. Patients must also consent to a blood sample for central genomic assessment using the BRACAnalysisCDx test by Myriad Genetics, except for patients who already have evidence of BRCA1/2 mutation by MYRIAD BRCAnalysisCDx post 2016. Blood samples for central BRCA status: collect two 10 mL samples of blood into appropriately labeled tubes at screening; send to Myriad Genetics for analysis. See, Central Laboratory Manual and sample collection instructions contained in the provided kit. If positive gBRCA1/2 status has been confirmed by local test, patients may enroll and commence study treatment, provided all other inclusion/exclusion criteria are met and screening tests have been satisfactorily completed. In the event of discrepant results, where the local test is positive for gBRCA1/2 mutation and the central Myriad BRACAnalysis test is negative, the decision on further continuation on trial will be decided by the investigator and discussed with the sponsor based on a risk-benefit evaluation.

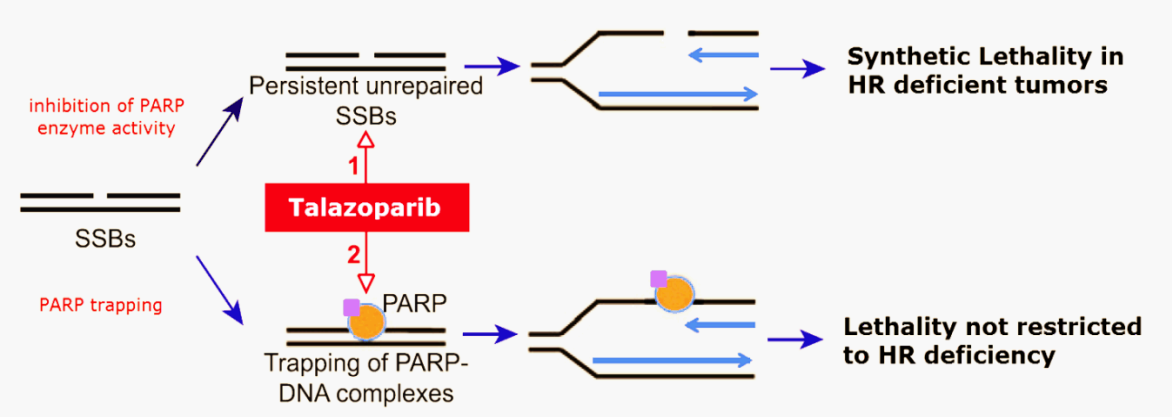
1. INTRODUCTION

Talazoparib (also known as PF-06944076, MDV3800, BMN 673) is being investigated for the treatment of patients with gBRCA-positive, HER2 negative breast cancer. A comprehensive review of talazoparib may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB), provided by Pfizer and published August 2018. Investigators are to review this document prior to initiating this study.

1.1. Mechanism of Action/Indication

Talazoparib is a potent, orally bioavailable, small molecule PARP inhibitor in development for the treatment of a variety of human cancers. PARP inhibitors, including talazoparib, exert cytotoxic effects via 2 mechanisms: (1) inhibition of PARP1 and PARP2 catalytic activity, and (2) PARP trapping, a process in which PARP protein bound to a PARP inhibitor does not readily dissociate from DNA (deoxyribonucleic acid), thereby preventing repair, replication, and transcription.[25]

Figure 2. Dual Cytotoxic Mechanisms of PARP Inhibitors



Source: Adapted from Reference.[25]
PARP = poly (adenosine diphosphate-ribose) polymerase; DNA= deoxyribose nucleic acid; hR=homologous recombination.
Inhibition of PARP catalytic activity (upper pathway) interferes with the repair of single-strand breaks, leading to replication fork damage that requires homologous recombination DNA repair for cell survival. Trapping of PARP–DNA complexes with PARP inhibitor (lower pathway; PARP inhibitor represented by■) also leads to replication fork damage with more DNA repair processes required for cell survival.

Single agent talazoparib treatment has demonstrated potent antitumor effects in tissue culture studies, mouse tumor xenograft models, and in Phase 1 studies in patients with solid tumors. Talazoparib has also been shown to enhance the cytotoxic effects of DNA damaging chemotherapy,[18,19] including temozolomide and irinotecan, in both in vitro and in vivo preclinical models.

The main nonclinical toxicology findings with talazoparib were early hematologic changes and subsequent bone marrow and lymphoid organ depletion; focal atrophy and degeneration of the testes, epididymis, and seminiferous tubules; and dose-dependent apoptosis/necrosis in the gastrointestinal (GI) tract, ovarian follicular atresia, and liver after repeat-dose administration of talazoparib. These findings are consistent with the exaggerated pharmacology of talazoparib and its tissue exposure pattern. The hetamaologic and male reproductive organ findings occurred at sub-therapeutic exposure whereas the GI, ovarian and liver-related changes occurred at higher therapeutic exposure margins. The hematologic findings were generally reversible and the early hematologic changes represent sensitive and early markers of target organ toxicity. Talazoparib is clastogenic in genetic toxicology evaluations. Talazoparib caused fetal malformations, structural variations and death of fetuses in an embryo-fetal development study in rats, in line with its clastogenic profile.

Talazoparib is being investigated for the neoadjuvant treatment of early HER2 negative, gBRCA1/2 mutation positive breast cancers. Talazoparib has previously been investigated in both a Phase 2 study (673-201; ABRAZO) and in a Phase 3 study (673-301; C3441009; EMBRACA) involving gBRCA mutation patients with locally advanced and/or metastatic breast cancer compared with physician's choice of capecitabine, eribulin, gemcitabine, or vinorelbine.

1.2. Background and Rationale

1.2.1. Breast Cancer

Breast cancer is the second leading cause of cancer-related death in women, despite improvements in screening and treatment regimens. The American Cancer Society estimates that in 2017, approximately 2470 men and 252,710 women will be diagnosed with breast cancer, and approximately 460 men and 40,610 women will die due to the disease.[26]

1.2.2. Triple Negative and Germline Breast Cancer Susceptibility Gene 1 or 2 Positive Breast Cancer

Twelve to twenty percent of breast cancers are categorized as triple-negative. TNBC is defined by the lack of protein expression of both estrogen receptor (ER) and progesterone receptor (PR), combined with an absence of HER2 receptor over-expression.[27] Six different molecular subtypes of breast carcinoma have been identified. Basal-like breast cancer is defined by the molecular phenotype of the tumor, as measured by complementary DNA (cDNA) microarrays; approximately 75% of TNBCs are basal-like.[28] The basal-like subtype is associated with a BRCA mutation in 11-42% of cases.[29]

Breast cancer is a biologically diverse and genetically heterogeneous disease.[1,2] Breast cancer susceptibility gene 1(BRCA1) and breast cancer susceptibility gene 2 (BRCA2) are key components in the repair pathway for DNA double strand breaks (Campeau et al, 2008),[3] and mutations in these genes account for 20% to 25% of hereditary breast cancers and 5% of all breast cancers.[4] A substantial portion of patients with gBRCA mutated breast cancer have hormone receptor-positive disease, including 20-30% of gBRCA1 carriers and 45-72% of gBRCA2 carriers.[5] In the United States, women in the general population have a 12% lifetime-risk of developing breast cancer.[30] In contrast, 55% to 65% of women who

inherit a BRCA1 mutation and approximately 45% of women who inherit a BRCA2 mutation will develop breast cancer by age 70.[31,32]

Prognosis and best treatment practices in patients with breast cancer with germline BRCA1 or BRCA2 mutations have largely been characterized in retrospective studies from single institutions.[33] When compared to sporadic primary breast cancer, BRCA1 disease is more likely to be hormone receptor negative and BRCA2 disease is more likely to be hormone receptor positive.[33,34] BRCA1 and BRCA2 breast cancers have been reported to be higher grade and higher stage and to have more extensive and extracapsular lymph node involvement compared to non-BRCA cancers.[33,35] Well-known prognostic and predictive factors for breast cancer include HR and HER2 expression.[36] ER negative, progesterone receptor negative, HER2 negative tumors, known as HER2 negative breast cancer, have a poor prognosis. Metastatic TNBC has the worst prognosis of all breast cancer subtypes, with a median PFS of 3 to 5 months and a median overall survival of <12 months.[37-40]

BRCA mutations can be present regardless of HR and HER2 status. Women who have BRCA1 mutations are more likely to develop TNBC than those who have BRCA2 mutations.[41] The choice of treatment is informed by the tumor receptor status at the time of initiation as tumor characteristics can evolve over time. Investigational treatments based on the BRCA mutation status are being explored. The FDA granted approval to the PARP inhibitor olaparib for the treatment of germline BRCA mutated, HER2 negative metastatic breast cancer in January 2018.

TNBC is a current focus due to poor prognosis and limited treatment options. In comparing the low dose cyclophosphamide, doxorubicin, fluorouracil (CAF) regimen from CALGB8541 to the dose dense regimen of doxorubicin, cyclophosphamide followed by paclitaxel (AC-T) in CALGB974110, the relative reduction in risk of recurrence was 55% for ER negative tumors, and 26% in ER positive tumors. The absolute improvement in risk of recurrence at 5 years was 22.8% for ER negative tumors and only 7% for ER positive patients treated with tamoxifen. However, the rate of recurrence remains high, with poor OS rates. Thus, a significant unmet medical need remains for new therapeutic options for women with TNBC. These patients, due to the loss of ER, PR, and HER2 target receptors, do not respond well to hormonal or trastuzumab-based therapy; traditionally, the options have been surgery or chemotherapy, individually or in combination. Retrospective neoadjuvant subject series have suggested that primary breast cancer in BRCA1 carriers is platinum-sensitive and relatively unresponsive to anthracyclines and/or taxanes[9] while other studies have found that BRCA1 is relatively responsive to anthracyclines and/or taxanes while BRCA2 disease is less responsive than sporadic primary breast cancer to these drug classes.[10]

1.2.3. Neoadjuvant Therapy For Breast Cancer

Neoadjuvant therapy was traditionally used for inoperable cancers; however, in recent years there has been a paradigm shift, and neoadjuvant therapy is used more frequently in early breast cancer (EBC). Large studies have demonstrated comparable response rates when compared with adjuvant systemic therapy.[42]

Neoadjuvant therapy offers a number of benefits, including down-staging of tumors to allow for breast conserving surgery (BCS) and rapid assessment of response to therapy. This could potentially expedite development and treatments for EBC.

1.2.4. Neoadjuvant Therapy For Triple Negative And Germline Breast Cancer Susceptibility Gene Positive Breast Cancer

Neoadjuvant therapy with platinum agents has yielded promising results. A Phase 2 study conducted by Garber et al.[43] evaluated cisplatin given as a single agent for four cycles to TNBC patients with stage 3 or 4 progression. The overall pCR was 22%. Seven percent of the women in the study were BRCA1 carriers; all achieved a pCR. There is consistent evidence to show that 10 to 20% of patients with TNBC who would not experience pCR following a taxane/anthracycline treatment regimen, will achieve pCR when platinum is added to the regimen.

The Geparsixto (NCT01426880) and CALBG (NCT00632853) trials were 2 randomized studies assessing the addition of platinum-based chemotherapy (CT) to neoadjuvant regimens in a TNBC patient population (n=400 to 600). Treatment regimens included taxol and doxil + platinum weekly in the Geparsixto trial, and taxol + carboplatinum 3 weekly followed by dose sense anthracyclines in the CALBG trial. pCR rates were 53% vs. 37% and 54% vs. 41% in TNBC. The pCR rate in the gBRCA subset of the Geparsixto trial was 61.7% vs. 50%. However, since increased rates of toxicity were observed as carboplatinum was added to standard chemotherapy regimens, it is not a single agent option.

1.2.5. Neoadjuvant Therapy for ER Positive Germline Breast Cancer Susceptibility Gene Positive Breast Cancer

A substantial portion of patients with gBRCA mutated breast cancer have hormone receptor-positive disease, including 22% of gBRCA1 carriers and 77% of gBRCA2 carriers.[5]

There is an unmet need for more effective therapies for gBRCA mutated hormone receptor positive breast cancer as such patients are considered to have a higher risk for recurrence than patients without gBRCA mutations as follows: Hormone receptor positive breast cancer is frequently characterized by a higher grade in gBRCA2 carriers than in noncarriers.[5]

- The rate of high recurrence score (RS) Oncotype Diagnostics (DX; Genomic Health, http://www.oncotypedx.com/ recurrence score) was approximately 3-fold higher in patients with gBRCA mutated estrogen receptor positive tumors compared with the general breast cancer population. This suggests that hormone positive breast cancer in BRCA carriers may differ molecularly from that in noncarriers.[5]

PARP inhibitors have demonstrated a clinical benefit in gBRCA mutated hormone receptor-positive breast cancer in both early and advanced settings.[44-46] After 6 months of neoadjuvant talazoparib monotherapy in neoadjuvant talazoparib expansion Study NCI02282345, patients with gBRCA mutated hormone receptor positive breast cancer had a pCR rate of 3/5 (60%) and a combined RCB 0+1 rate of 4/5 (80%).[22] Although based on a limited sample size, this promising pCR rate is substantially higher than that reported for

patients with hormone receptor positive early breast cancer who received chemotherapy[44-46] and is similar to the pCR rates obtained by adding PARP inhibitors or carboplatin to conventional chemotherapy for the treatment of patients with early TNBC.[44-46] These results suggest talazoparib monotherapy may benefit the gBRCA mutated hormone receptor positive subgroup of patients with early breast cancer as well.

The clinical benefit of neoadjuvant PARP inhibitors seen in the small groups of patients with hormone receptor positive tumors in studies of gBRCA mutated early breast cancer is supported by the demonstrated clinical benefit in larger groups of patients in advanced settings.[46,21]

Data from the Phase 3 EMBRACA study and Phase 2 ABRAZO study demonstrated the benefit of talazoparib monotherapy in gBRCA mutated, hormone receptor positive HER2 negative advanced breast cancer.

- EMBRACA: Patients with hormone receptor positive advanced breast cancer comprised approximately 60% of the randomized patients. In the prespecified subgroup analyses of the primary PFS endpoint, the hormone receptor positive subgroup had a hazard ratio of 0.47 (95% CI: 0.32, 0.71), and the TNBC subgroup had an HR of 0.60 (95% CI: 0.41, 0.81). A significant improvement in ORR was also observed in both subgroups. For the hormone receptor positive subgroup, ORR was 63.2% in the talazoparib arm versus 37.9% in the PCT arm, with an odds ratio of 2.89 (95% CI: 1.43, 4.83) p=0.0012). For TNBC, ORR was 61.8% in the talazoparib arm versus 12.5% in the PCT arm with an odds ratio of 11.89 (95% CI: 4.54, 41.37; p<0.0001).

- ABRAZO: For patients with hormone receptor positive advanced breast cancer, ORR was 26.3% (5/19 patients) in Cohort 1 (platinum pretreated patients) and 31% (9/29 patients) in Cohort 2 (patients with 3 or more prior non-platinum-containing cytotoxic regimens). For patients with TNBC, the ORR was 17.2% (5/29 patients) in Cohort 1 and 66.7% in Cohort 2 (4/6 patients).

The gBRCA mutational status appears to be a stronger biomarker of efficacy for talazoparib than hormone-receptor status based on the consistency of the treatment effect between patients with hormone receptor positive breast cancer and those with TNBC in EMBRACA and ABRAZO. Deleterious gBRCA mutations cause DNA damage repair deficiencies, making cells vulnerable to targeted therapy with PARP inhibitors, regardless of disease stage.

1.2.6. Pathological Complete Response as an Endpoint in Neoadjuvant Trials

Von Minckwitz[45] conducted a pooled analysis of 12 international neoadjuvant breast cancer trials. One of the key objectives was to determine the association between pCR and long-term outcome in terms of EFS and OS. In the TNBC patients, there was a 76% reduction in events and an 84% reduction in mortality when patients achieved a pCR, further supporting pCR as an endpoint for TNBC. The impact of molecular subtype on the pCR shows that more aggressive types of cancers, ie, TNBCs, achieve a higher percentage of pCR than HER positive breast cancers. Perjeta (pertuzumab, NCT01855828), first approved

in 2012, utilized pCR as a primary endpoint. Neoadjuvant pertuzumab and trastuzamab, administered concomitantly with weekly paclitaxel and followed by 5-fluorouracil/epirubicin/cyclophosphamide, resulted in a 78% pCR rate in ER negative/HER2 positive cancers (the pCR rate was substantially lower in ER positive cancers). This pCR rate is among the highest reported in the literature.[49]

The FDA Guidance Document '*Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval*' published in October 2014[50] supports the use of pCR as an endpoint in the neoadjuvant setting. Per the Guidance, pCR is defined as:

1. The absence of residual invasive cancer in the breast and axillary lymph nodes on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ie, ypT0/Tis ypN0 in the current AJCC staging system); or

2. The absence of residual invasive and in situ cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ie, ypT0 ypN0) in the current AJCC staging system).

1.2.7. Poly(ADP Ribose) Polymerase Inhibition

PARP1 and PARP2 play important roles in DNA repair.[51,52] Following DNA damage, PARP1 and PARP2 bind to single-stranded DNA breaks, cleave nicotinamide adenine dinucleotide, and attach multiple ADP-ribose units to the target protein, including itself.[53-56] The outcome is a highly negatively charged protein, which leads to the unwinding of the DNA strands and recruitment of proteins to repair the damaged DNA through the base-excision repair process. When PARP1 and PARP2 are inhibited, single-strand DNA breaks persist, resulting in stalled replication forks and conversion of single-strand breaks into double-strand breaks. These breaks must be repaired by homologous recombination or non-homologous end joining or they may become lethal. Thus, inhibition of PARP catalytic activity results in synthetic lethality as defects in homologous recombination DNA repair prevent double strand breaks from being repaired, thereby killing the cell, including cancer cells.

In addition, PARP inhibitors bind to PARP-DNA complexes (ie, become trapped), thereby inhibiting DNA repair, replication, and transcription, which may also be cytotoxic to cancer cells. Although other PARP inhibitors possess both activities, in vitro studies demonstrated that talazoparib is a more potent PARP trapper than other PARP inhibitors in clinical development.[57,58]

1.2.8. Poly (ADP Ribose) Polymerase Inhibitors as a Potential Targeted Therapeutic in Triple Negative Breast Cancer with Germline Breast Cancer Susceptibility Gene Mutations

There is mounting evidence that germline BRCA1/2 breast cancers, besides having increased sensitivity to platinum agents, are also sensitive to PARP inhibitors.

In a phase 1 trial, the PARP inhibitor olaparib (NCT00516373; 10 to 600 mg twice a day) treatment of solid tumors of patients with breast cancer with no gBRCA mutations vs. those patients with gBRCA mutations, resulted in an objective response rate (ORR) of 15% and 33%, respectively.[1] Tutt et al,[15] in a phase 2 trial (NCT00494234) of single agent olaparib in patients with breast cancer with BRCA1/2 mutation and advanced disease, investigated two dose levels (cohort 1: 400 mg twice daily [bd] and cohort 2: 100 mg bd) and demonstrated an ORR of 42% and 25%, respectively. Progression free survival (PFS) was 5.7 and 3.8 months for Cohorts 1 and 2, respectively. A phase I study of niraparib (NCT00749502; 30 400 mg once a day) for treatment of solid tumors resulted in an ORR of 40% in patients with breast cancer with gBRCA mutations vs. 18% in the general breast cancer population.[16] Lastly, a first in human trial of oral talazoparib (NCT01286987; 25 1100 ug/day) resulted in an ORR of 65% and 33% in solid tumors of gBRCA patients with ovarian cancer or breast cancer, respectively.[17]

Olaparib, which was approved by the FDA in 2014 for patients with advanced ovarian cancer with gBRCA mutations, was also assessed during a Phase 3 study (OlympiAD) in metastatic gBRCA mutated breast cancer. This trial included patients with HER2 negative, metastatic breast cancer that were either HR positive or triple negative; a subgroup of the patient population (approximately 50%) were defined as TNBC. In the OlympiAD study, 205 patients with gBRCA mutated breast cancer were treated with olaparib (300 mg orally twice daily), compared to 91 patients (6 were not treated) treated with physician's choice of chemotherapy (capecitabine, vinorelbine, or eribulin). Seventy-one percent had been previously treated with anthracycline and a taxane in either an adjuvant or metastatic setting. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) score of 0 to 1; gBRCA1/2 mutations; and histologically or cytologically confirmed breast cancer with evidence of metastatic disease. Prior exposure to platinum was allowed, as long as no breast cancer progression occurred on treatment or if given in an adjuvant or neoadjuvant setting at least 12 months before study commencement (28%). The hazard ratio for PFS was 0.58 (95% CI; range 0.43 to 0.80; $p<0.001$; median of 7 months in the olaparib group vs. 4.2 months in the chemotherapy group). The objective response rate was 59.9% in the olaparib arm vs. 28.8% in the treatment of physician's choice (TPC) arm. Grade ≥3 adverse events (AEs) occurred in 36.6% and 50.5% of the olaparib and TPC arms, respectively. Mean change from baseline in global health-related quality of life (HRQoL, EORTC-QLQ-C30) across all timepoints favored olaparib (difference vs TPC 7.5; 95% CI 2.48, 12.44; $p=0.0035$).[59] In summary, olaparib provided significant benefit over standard therapy among patients with gBRCA muatated breast cancer.

The data for talazoparib in TNBC patients with gBRCA positive mutations are detailed in Section 1.3.1.

1.3. Summary of Relevant Clinical Experience with Talazoparib

Talazoparib is a potent and specific inhibitor of PARP1 and PARP2 that play important roles in DNA repair.[60,61] PARP inhibitors exert cytotoxic effects by 2 mechanisms: inhibition of PARP catalytic activity and PARP trapping. Inhibition of PARP catalytic activity results in persistent single strand DNA breaks that require homologous recombination mediated DNA repair for survival. PARP trapping prevents a talazoparib bound PARP protein complex from readily dissociating from DNA, thereby inhibiting DNA repair, replication, and transcription, resulting in double strand DNA breaks and consequent cytotoxicity.[62] PARP inhibitors induce synthetic lethality in tumor cells that bear mutations and/or deletions in genes involved in homologous recombination or other DNA repair pathways. In BRCA1 and BRCA2 deficient cells, treatment with a PARP inhibitor results in cell cycle arrest and apoptosis.[63]

Talazoparib is more potent at inducing single agent synthetic lethality of BRCA1 and BRCA2 deficient tumor cells in vitro than any other PARP inhibitors reported to date.[64] Talazoparib inhibited growth of MX 1 human breast cancer cells (BRCA1 deficient) and Capan 1 pancreatic cancer cells (BRCA2 deficient), with 50% inhibitory concentration (IC50) values of 0.3 nM and 5.0 nM, respectively.[65] The talazoparib IC50 for growth inhibition of Capan 1 cells was 50 to >2000 fold lower than the other PARP inhibitors tested. This superior cytotoxicity profile is potentially linked to the robust PARP trapping activity of talazoparib. Consistent with its cytotoxic effects in tissue culture studies, talazoparib demonstrated antitumor activity in xenograft tumor models. Talazoparib administered at 0.33 mg/kg/day inhibited the growth of BRCA1 mutant MX 1 breast cancer xenografts in mice, while the same model proved refractory to olaparib administered at 100 mg/kg/day. These in vitro and in vivo activities suggest that talazoparib may have clinical activity in patients with BRCA mutated breast cancer.

As of 30 Nov 2017, (the cutoff date for the most recent Development Safety Update Report),[66] approximately 798 patients have received talazoparib in company sponsored studies in hematologic malignancies and solid tumors. Studies in solid tumors include a Phase 1 study (PRP-001) in advanced or recurrent solid tumors, a Phase 1 study in advanced malignancies (PRP-002), a Phase 2 study (673-201, C3441008, ABRAZO) in locally advanced and/or metastatic patients with breast cancer with a germline BRCA defect, a Phase 3 study (673-301, EMBRACA) in locally advanced or metastatic breast cancer with a germline BRCA defect, a Phase 1 hepatic impairment study (MDV3800-02), a Phase 1 absorption, distribution, metabolism and excretion (ADME) study (MDV3800-03), a Phase 1 study on cardiac re-polarization (MDV3800-14), a Phase 1 renal impairment study (NCT02997163), and a Phase 2 response rate study in men with DNA repair defects and metastatic castration-resistant prostate cancer (TALAPRO-1).

In Study PRP-001, a Phase 1, first-in-human, single-arm, open-label dose-escalation study of once daily talazoparib (BMN 673) in patients with advanced or recurrent solid tumors with DNA repair deficiencies, a total of 110 patients were treated with talazoparib at doses ranging from 0.025 to 1.1 mg/day. During the dose-escalation phase of the study, 2 of the 6 patients enrolled in the talazoparib 1.1 mg/day dose level experienced a dose-limiting toxicity: one was Grade 4 thrombocytopenia, the other was Grade 3 thrombocytopenia

requiring >5 days off study treatment. Therefore, 1 mg/day was considered the maximum tolerated dose and recommended Phase 2 dose. Between the dose-escalation and dose-expansion portions of the study, a total of 77 patients were treated with talazoparib at the 1 mg/day dose level in Study PRP-001 which was generally well tolerated and warranted further evaluation in patients with solid tumors with DNA repair deficiencies. As a result, talazoparib has been dosed at 1 mg/day in subsequent studies in patients with solid tumors, including the breast cancer studies ABRAZO, EMBRACA, and currently ongoing investigator-initiated research.

The first indication for talazoparib is expected to be in patients with deleterious germline BRCA1 or BRCA2 mutations and HER2 negative locally advanced and/or metastatic breast cancer, pending results of study (673-301, EMBRACA). Studies include a phase 1 study (PRP-001) in advanced or recurrent solid tumors, a study (PRP-002) in patients with hematologic malignancies, a Phase 2 study (673-201, ABRAZO) in locally advanced and/or metastatic breast cancer, and a Phase 3 study (673-301, EMBRACA) in locally advanced and/or metastatic breast cancer. Results from company-sponsored studies are summarized in the following sections.

1.3.1. Efficacy

A phase 1 clinical study supports the efficacy of talazoparib at 1 mg/day.

PRP-001 is a phase 1, open-label, safety, pharmacokinetics, and dose-escalation (0.025-1.1 mg/day) and expansion (1 mg/day) study of talazoparib monotherapy in 110 patients with advanced or recurrent solid tumors with DNA repair deficiencies. As of the data cutoff date of 31 Jan 2018, objective responses (complete response [CR] or partial response per revised response evaluation criteria in solid tumors (RECIST) 1.1 were observed in 7 of 14 patients (50%) with breast cancer and 5 of 12 patients (41.7%) with ovarian/primary peritoneal cancer with deleterious germline BRCA mutations; clinical benefit (CR, PR, or stable disease ≥24 weeks) was observed in 12 of 14 patients (85.7%) and 8 of 12 patients (66.7%), respectively.

Study 673-201 (ABRAZO) is a Phase 2, 2-stage, 2-cohort study of talazoparib in patients with germline BRCA mutation and locally advanced and/or metastatic breast cancer. ABRAZO is investigating the clinical efficacy and safety of single-agent talazoparib in 83 heavily pre-treated gBRCA positive patients with advanced breast cancer. The primary endpoint was ORR by independent radiology review. Cohort 1 consisted of 49 patients who previously responded to platinum-based chemotherapy and subsequently developed disease progression. A 21% ORR (95% confidence interval [CI]: 10-35) was observed in this group of patients. Cohort 2 consisted of 35 patients who developed disease progression following at least three lines of non-platinum-based therapy. This group of patients had a 37% ORR (95% CI: 22 to 55). Safety data for talazoparib as monotherapy are available from Phase 1, 2, and 3 studies in patients with advanced cancer. As of 31 January 2018, the confirmed objective response rate (CRs and pRs) was 20.8% for cohort 1 (prior platinum treatment, 95% confidence interval: 10.47, 34.99), including 2 CRs (4.2%), and 37.1% for Cohort 2 (3+L, non-prior platinum treatment, 95% CI: 21.47, 55.08) per independent central radiology assessment. The objective response rate across both cohorts was 27.7% (95% CI: 18.45,

38.62), demonstrating clinically meaningful responses in this population with a poor prognosis and a high unmet medical need. TNBC/HR positive incidence in Cohorts 1 and 2 was 59%/41% and 17%/83%, respectively; while ORR by IRF for TNBC/HR positive was 26%/29%, respectively.[47]

Aggregate safety data from 502 patients treated with open-label 1 mg/day talazoparib monotherapy (PRP-001, 673-201, 673-301, MDV3800-13, and MDV3800-14); data as of 31 January 2018) provide the basis for the most common treatment emergent AEs in patients with solid tumors. The most common AEs associated with talazoparib (>20%) were myelosuppression (anemia, neutropenia), gastrointestinal toxicity (nausea, diarrhea, vomiting, constipation), fatigue, alopecia, headache, and decreased appetite. The most common (>5%) Grade 3 or 4 AEs and SAEs were associated with myelosuppression. A total of 23 of 502 patients had a AE that led to death (8 associated with malignancies [1 pancreatic carcinoma patient; the other 7 malignancies were due to disease progression: 3 ovarian cancer patients, 2 breast cancer patients, and 1 metastatic breast cancer patient with bronchopneumonia]; 2 dyspnea; 2 general physical health deterioration; 3 disease progression; and 1 each lung infection, cerebral hemmorage, cerebrovascular incident, fatigue, liver disorder, neurological symptoms, respiratory failure, and veno-occlusive liver disease). Of these, only the latter (reported in one patient in study 673-301) was assessed as related to study drug by the investigator. The permanent discontinuation rate was relatively low (20 of 502 patients, 4%) due to AEs of anemia, increased ALT and accidental overdose, increased AST, bradycardia, metastatic breast cancer, cerebral hemorrage, dyspnea, glioblastoma multiforme, headache, metastases to meninges, muscular weakness, neutropenia, obstructive airways disorder, thrombocytopenia, transient ischemic attack, and vomiting.

Another study in the advanced breast cancer setting conducted by Litton et al. was recently published in the New England Journal of Medicine.[21,22] This study (EMBRACA, NCT01945775) was a randomized, open-label, Phase 3 trial in which patients with advanced breast cancer and a germline BRCA1/2 mutation were assigned, in a 2:1 ratio, to receive talazoparib (1 mg once daily) or standard single-agent therapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine in continuous 21-day cycles). The primary endpoint was progression-free survival. Of the 431 patients who underwent randomization, 287 were assigned to receive talazoparib and 144 were assigned to receive standard therapy. Progression-free survival was significantly longer in the talazoparib group than in the standard-therapy group (hazard ratio for disease progression or death, 0.54; 95% CI, 0.41 to 0.71; p<0.001; medians 8.6 months vs. 5.6 months). The hazard ratio for overall survival based on interim analysis at the time of the final progression-free survival analysis was 0.76 (95% CI, 0.55 to 1.06; p=0.11 [57% of projected events]; medians 22.3 months vs. 19.5 months). The objective response rate was higher in the talazoparib group than in the standard-therapy group (62.6% vs. 27.2%; odds ratio, 5.0; 95% CI, 2.9 to 8.8; p<0.001). In all clinically-relevant subgroups, a consistent PFS benefit in favor of talazoparib was observed in comparison with physician's choice of treatment (PCT), regardless of hormone receptor status (hormone receptor positive [HR positive]: hazard ratio 0.47, 95% CI, 0.32 to 0.70; or TNBC: hazard ratio 0.60, 95% CI, 0.41 to 0.87) BRCA mutation subtype, history of central nervous sytem (CNS) metastasis, visceral/non-visceral

disease, or number of prior cytotoxic chemotherapies for advanced disease. Complete response was seen in 5.5% of patients with talazoparib therapy vs zero patients receiving PCT, and partial response was seen in 57.1% vs 27.2%, respectively. In an exploratory analysis, time to end of first post-study therapy was longer with talazoparib (hazard ratio 0.68; 95% CI; 0.51 to 0.91).

In terms of hematologic toxicities, 8 of 20 (40%) patients had Grade 3 anemia. There were no patients with Grade 4 anemia. There was one case of Grade 4 thrombocytopenia. Neutropenia occurred in 4 patients at Grade 2 (20%) and Grade 3 in 3 (15%) patients.

Talazoparib was generally well tolerated, and few adverse events (excluding progressive disease) led to permanent treatment discontinuation (5.9% in talazoparib arm vs 8.7% in PCT). Most non-hematologic toxicities were lower-grade, and the more common hematologic toxicities were managed by dose interruption or dose reduction and supportive care as needed.

An investigator-initiated research (IIR) study at MD Anderson Cancer Center titled "Neoadjuvant Talazoparib for Patients With a BRCA Deleterious Mutation" explored the feasibility of neoadjuvant talazoparib in a two part study (NCT02282345). Part 1, which evaluated a lead-in of 2 months of talazoparib single agent followed by standard chemotherapy and surgery, is complete and was accepted for publication in NPJ Breast Cancer.[23] Decreases in tumor volume (as assessed by the Investigator) occurred in 13 out of 13 patients following 2 months of talazoparib monotherapy (1 mg). The median tumor volume decrease after 2 months of treatment with talazoparib was 88% (range of 30-98%). Notably, all TNBC patients achieved either RCB-0 or RCB-1 following completion of the protocol assigned therapy and surgery. In this pilot study, talazoparib was well tolerated with no Grade 4 or 5 toxicities observed, and only one patient required dose reduction due to Grade 3 neutropenia. Following these data on efficacy and tolerability, Part 2 of the study was opened and evaluated 24 weeks of talazoparib monotherapy followed by surgery with no additional chemotherapy. This part of the study enrolled 20 patients total who received talazoparib monotherapy for 6 months followed by surgery and assessment of pCR. All patients were BRCA positive and the majority was stage 2 or 3; most patients had triple negative breast cancer. pCR to single agent talazoparib were 10/19 = 53%, (95% CI = 32%, 73%). Residual Cancer Burden was also evaluated: RCB 0 (no RCB) + RCB 1 (minimal residual disease) was 12/19 = 63%, 95% CI = 41%, 81%. TNBC/HR positive incidence in Cohorts 1 and 2 was 59%/41% and 17%/83%, respectively; while ORR by IRF for TNBC/HR positive was 26%/29%, respectively.[54] There were 14 patients in the TNBC cohort. Of those patients, 7 (50%) patients had RCB-0, 1 (7.4%) patient had RCB-1, 4 (28.5%) patients had RCB- 2 and 2 (14.2%) patients had RCB-3. Of note, pCR occurred in both metaplastic carcinoma and lobular carcinoma. Talazoparib was well tolerated with acceptable adherence and manageable toxicities.

For non-hematologic toxicities, most were Grade 1 and 2. The most common toxicities occurring in >50% of patients were nausea, fatigue, and alopecia. Nineteen (19) of 20 patients completed 6 months of therapy; one patient completed 5 months and then received chemotherapy prior to surgery. Two patients had dose reductions to 0.75 mg,

6 patients reduced to 0.5 mg, and one patient had a dose reduction to 0.25 mg. All dose reductions were due to hematologic toxicities.

The findings from this study demonstrate promising efficacy for talazoparib in the neo-adjuvant gBRCA positive early breast cancer setting. Talazoparib is the first single targeted therapy to achieve pCR in BRCA positive patients, including TNBC. This study warrants the larger confirmatory trial (C3441020).

1.3.2. Pharmacokinetics and Metabolism

The PK of talazoparib as a single agent was evaluated in 142 adult patients with cancer, including 109 patients with solid tumors (PRP-001) and 33 with hematologic malignancies (PRP-002). Doses of 0.025 mg to 2 mg were administered orally as a single dose or as once-daily doses. This dose range bracketed the 1 mg/day dose used in ongoing safety and efficacy studies and provided a framework for assessing dose linearity. As the PK of talazoparib was similar in patients with solid tumors and hematologic malignancies, and no differences were apparent between males and females, the results are summarized collectively.

Oral absorption of talazoparib was rapid and independent of dose after administration of single or once-daily doses. Peak talazoparib concentrations were generally reached approximately 1 to 8 hours post-dose. Exposure increased approximately dose-proportionally with increasing doses. At 1 mg/day, the mean half-life was approximately 2 days; the mean apparent volume of distribution (V/F) was 415 L, which may suggest extensive extravascular distribution. Steady state was reached in approximately 2 to 3 weeks with daily administration.

Apparent oral clearance (CL/F) of talazoparib appeared to be dose linear, with a mean CL/F across doses of approximately 5 liters per hour (L/h). Renal excretion was a major elimination pathway for unchanged parent talazoparib. Following oral administration, 44% to 90.6% of the dose was recovered in urine as unchanged parent drug over 24 hours at steady state for doses up to 1 mg/day. Mean renal clearance ranged from 1.38 L/h to 4.96 L/h independent of dose, suggesting linear urinary elimination kinetics.

A preliminary population PK analysis using data from patients in studies PRP-001 and PRP-002 assessed the effects of renal function on the PK of talazoparib. The talazoparib CL/F in patients with mild renal impairment (creatinine clearance [CL_{CR}] 60-89 mL/min) was similar compared with patients with normal renal function (CL_{CR} ≥90 mL/min). In patients with moderate renal impairment (CL_{CR} 30-59 mL/min), the talazoparib CL/F was decreased by 44% from normal, resulting in higher talazoparib exposure.

Talazoparib does not induce or inhibit cytochrome P450 (CYP) enzymes or transporters and is therefore unlikely to demonstrate drug drug interaction liabilities. However, talazoparib is a substrate for P-gp and breast cancer resistance protein (BCRP). In a clinical drug drug interaction study, coadministration of talazoparib with a strong P gp and BCRP inhibitor (itraconazole) resulted in a 50% increase in talazoparib exposure (AUC_{24}), while coadministration of talazoparib with an inducer (rifampin) caused no change in exposure.

Talazoparib is eliminated via renal excretion with minimal metabolism. Talazoparib does not cross the blood brain barrier, so neuropsychiatric adverse events are not expected.

Talazoparib is not mutagenic, but similar to other PARP inhibitors, is clastogenic in vitro in peripheral blood lymphocytes and in vivo in a rat bone marrow micronucleus assay. The inhibition of the PARP catalytic activity is potentially linked to the clastogenic activity of talazoparib. In line with its clastogenic property, talazoparib caused fetal malformations, structural variations, and death in an embryo fetal development study in rats.

The main nonclinical toxicology findings at subtherapeutic exposures of talazoparib were hematologic changes including pancytopenia, bone marrow hypocellularity, and lymphoid depletion. Findings in reproductive organs were focal atrophy and degenerative changes in the testes, epididymis, and seminiferous tubules. Additional changes included dose dependent apoptosis/necrosis in the gastrointestinal (GI) tract, ovarian follicular atresia, and liver after repeat dose administration of talazoparib. The findings in the ovary were observed at greater than 5-fold clinical margin. These findings are consistent with the exaggerated pharmacology of talazoparib and its tissue exposure pattern. The hematologic findings were generally reversible and the early hematologic changes represent sensitive and early markers of target organ toxicity.

1.3.3. Rationale for Talazoparib Dose

The doses of talazoparib in this protocol are supported by nonclinical studies and phase 1 studies in patients with advanced malignancies. Antitumor activity has been observed and warrants further exploration in a larger patient population. The expected adverse events with talazoparib include myelosuppression, gastrointestinal toxicity, and fatigue. Hepatotoxicity, febrile neutropenia, and neutropenic sepsis are potential risks per the investigator brochure, Section 7. The activity of talazoparib as monotherapy and in combination with other agents is being evaluated in multiple indications.

Talazoparib has demonstrated efficacy at a dose of 1 mg/day. Talazoparib 1 mg/day orally will be administered until completion of protocol assigned therapy, unacceptable toxicity, withdrawal of consent, or death. For patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] 30-59 mL/min/1.73 m^2) at screening, the starting dose will be 0.75 mg/day. The dose of 1 mg /day has been established as the recommended dose for adults with solid tumors in study PRP-001 (NCT01286987). Subsequently this dose has been used as the starting dose in studies 673-201 (ABRAZO), MDV3800-14, and 673-301 (EMBRACA) with a total number of approximately 403 patients having received talazoparib at 1 mg/ day.

1.4. Rationale for Study

Approximately 15% of all breast cancers are triple negative. They can be defined by the lack of estrogen, progesterone, and HER2 receptors. They are more commonly associated with younger women, pre-menopausal women of African American race and BRCA1 mutation carriers. Triple negative cancers are generally more aggressive in nature and associated with visceral and soft tissue disease.

The incidence of BRCA 1 and 2 mutations in patients with TNBC has been reported to be between 9.6 to 10.6%.[6,7] In a study of 469 TNBC patients, gBRCA1/2 mutation prevalence was also shown to vary by race: Ashkenazi Jewish (50%), Caucasian (33.3%), Asian (28.5%), African Americans (20.4%), and Hispanic (20%). The prevalence of genetic mutations also differed by age at diagnosis, with most patients <40 years (43.8 %) of age.

Various studies have demonstrated that triple negative breast cancers are associated with a poorer prognosis than luminal breast cancers. A Canadian series, including approximately 1600 triple negative cancers conducted by Dent, R et al.[8] demonstrated worse long term outcomes in terms of distant recurrence and death in triple negative tumors compared to non-triple negative tumors.

The standard of treatment for neoadjuvant treatment is variable, but mostly focuses on the use of anthracycline- taxane regimens. Other regimens used include adriamycin plus cyclophosphamide (AC). Cyclophosphamide methotrexate, and fluorouracil (CMF) is another option which offers less toxicity, however has a longer duration of therapy.

Platinum therapies have also shown efficacy in HER2 negative breast cancer, in particular germline BRCA mutant tumors as these tumors have defects in homologous recombination rendering them more susceptible to DNA cross linking agents such as platinums.

The Geparsixto and CALGB trials examined the efficacy of adding platinum to neoadjuvant regimens in triple negative breast cancer. In GeparSixto, the pCR rates (breast/axilla) increased from 36.9% to 53.2% and in the BRCA subgroup an increase in pCR by 25% (p=0.005). The CALGB/Alliance trial showed an increase in pCR with the addition of carboplatin for breast/axilla (54% vs 41%; p=0.0029).

Since these studies were underpowered for long term outcome, it is difficult to assess long term benefit. Therefore, the role for platinum therapy in TNBC still remains unclear and warrants further investigation in larger trials with examination of long term outcomes. There have been studies resulting in improved disease-free survival (DFS) in patients who achieved pCR with platinum agents and BRCA mutation. Frasci et al.[11] reported that in TNBC patients treated with eight cisplatin epirubicin paclitaxel weekly cycles, 62% showed pCR in both breast and axilla, and the projected 5 year DFS was 90% and 56% in pCRs and non pCRs, respectively.

The BRCA1 gene is expressed in several tissues, such as breast and ovarian tissue. Currently, more than 1600 mutations have been identified in the BRCA1 gene, and the majority of them promote frameshifts resulting in missense or non-functional protein. Women with BRCA1 mutations have an increased risk of developing breast and ovarian cancer, while men have a higher risk, to a lesser extent, of developing prostate cancer.[12]

BRCA2 does not share a high degree of sequence homology with other known genes, and the generated protein is comprised of regions with domains that are undefined.[13] Currently, more than 1800 mutations have been identified in BRCA2, that include frameshift deletions, insertions, or nonsense mutations that lead to premature truncation of proteins.

It has been demonstrated that BRCA1 and BRCA2 tumor suppressor genes perform a critical role in the response to cellular damage through activation of specific DNA repair processes and play an important part in DNA repair and as transcriptional regulators.[14]

Inhibition of PARP catalytic activity contributes to the process of synthetic lethality defined as a combination of two DNA repair pathway defects which may be lethal to the cell resulting in single-strand breaks that require homologous recombination DNA repair for survival. PARP inhibitors induce synthetic lethality in tumor cells containing mutations and/or deletions in genes involved in homologous replication or other DNA pathways, including BRCA1 and BRCA2.

Clinical trials have shown that PARPi are beneficial in the treatment of patients that are carriers of germline BRCA mutations.

Talazoparib is a potent, orally bioavailable, small molecule PARP inhibitor in development for the treatment of a variety of human cancers. Single agent talazoparib treatment demonstrates potent antitumor effects in tissue culture studies, mouse tumor xenograft models, and in Phase 1 studies in patients with solid tumors. Talazoparib has also been shown to enhance the cytotoxic effects of DNA damaging chemotherapy.[18,19]

Despite advances in the understanding of the biology of gBRCA associated TNBC, treatment options remain limited. PARPi, as well as platinum-based combination therapies, have emerged as regimens of potential interest and in particular therapy with single agent PARPi could present significant advantages of chemotherapy regimens through potentially improved tolerability.

The PARP inhibitor olaparib, which was approved by the FDA in 2014 for patients with advanced ovarian cancer with gBRCA mutations was assessed during a Phase 3 study (OlympiAD) in metastatic gBRCA mutated breast cancer. PFS was 7 months in the olaparib group vs. 4.2 months in the chemotherapy group (observed hazard ratio=0.58; 95% CI, 0.43 to 0.80; p=0.009). The objective response rate was 59.9% in the olaparib arm vs. 28.8% in the chemotherapy arm. Olaparib was determined to be effective against triple-negative breast cancers that arise in women with inherited, germline BRCA mutations (observed hazard ratio in the TNBC subgroup = 0.43).

The Phase 2 ABRAZO study[21] (NCT02034916), presented at American Society of Clinical Oncology (ASCO) 2017, demonstrated clinical activity of single agent talazoparib in advanced triple negative, germline BRCA mutant breast cancer. Talazoparib (1 mg/day) was administered following platinum-based therapy (Cohort 1) or ≥3 platinum-free cytotoxic-based regimens (Cohort 2) in TNBC, gBRCA1/2 mutation patients with locally advanced or metastatic breast cancer. TNBC/HR positive incidence in Cohort 1 and Cohort 2 was 59%/41% and 17%/83%, respectively. ORR by IRF for BRCA1/BRCA2 was 24%/34%, and ORR by IRF for TNBC/HR positive was 26%/29%. Talazoparib was well-tolerated in both cohorts.

The present study is a non-randomized Phase 2 study in gBRCA 1/2 positive early HER2 negative breast cancer which will evaluate the safety and efficacy of talazoparib in the neoadjuvant setting. It will also evaluate patient related outcomes [redacted] in this patient population.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 2. Objectives and Endpoints

Primary Objective:	Primary Endpoint:
• To evaluate the pCR to talazoparib after completion of 24 weeks of neoadjuvant therapy followed by surgery. pCR will be assessed by ICR.	• pCR by ICR after completion of 24 weeks of talazoparib followed by surgery post-neoadjuvant treatment defined as ypT0/Tis ypN0 (the absence of residual invasive cancer in the breast and the axillary lymph nodes on evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy).
Secondary Objective(s):	**Secondary Endpoint(s):**

• To evaluate pCR (breast and axilla) by investigator and pCR in breast only.
• RCB by ICR.
• To evaluate long term outcome by assessment of 3-year EFS and OS.
• To evaluate the safety and tolerability of talazoparib.
• To describe the steady-state PK of talazoparib in patients with gBRCA mutation-positive, HER2 negative breast cancer.
• To evaluate the following PRO:
  • Global health status/QoL, functioning, and symptoms (including nausea and vomiting);
  • Missed expected menstrual period; this objective captures the concept of fertility preservation through PRO, since there is a possible fertility sparing effect of talazoparib versus
	• pCR by investigator.
	• pCR (in breast) by ICR.
	• RCB by ICR.
	• EFS (estimated at 3 years).
	• OS (estimated at 3 years).
	• Type, incidence, severity (as graded by the NCI-CTCAE v4.03), seriousness and relationship of study medications to adverse events (AE) and any laboratory abnormalities.
	• PK of talazoparib using sparse sampling (Ctrough at limited timepoints).
	• Time to definitive deterioration in global health status/QoL per EORTC QLQ-C30.
	• Time to definitive deterioration in nausea and vomiting symptoms per EORTC QLQ-C30.
	• Change from baseline in global health status/QoL, functioning, and symptoms per EORTC QLQ-C30 and EORTC QLQ BR-23.
	• Proportion of patients with deterioration, improvement and no change in nausea and

chemotherapy.	vomiting symptoms. • Change in baseline in proportion of patients with missed expected menstrual period per PRO-CTCAE.
CCI [redacted]	[redacted]
[redacted]	[redacted]

3. STUDY DESIGN

This is a non-randomized, open-label, multi-center, single-arm, phase 2 efficacy and safety trial of talazoparib as neoadjuvant therapy in gBRCA1/2 positive early HER2 negative breast cancer. The trial is being conducted in the US only.

Approximately sixty total patients will be enrolled in the study and treated with talazoparib 1 mg QD for 24 weeks, followed by surgery and an assessment for pCR by central review. The trial will be considered a success if the posterior probability that the true pCR rate exceeds 45% is ≥80%. Once 28 evaluable patients are assessed for pCR, if 11 or less responses are observed, the predictive probability of the trial being successful at the full sample size is less than 10%, at which point the Sponsor would recommend stopping the study due to futility. If ≥12 responses are observed in the first 28 evaluable patients, the study will continue enrolling to 60 patients.

Patients will receive talazoparib 1 mg daily for 24 weeks, followed by breast surgery, which should occur within 4 to 6 weeks (no longer than 6 weeks) of the last dose. If hematological toxicity is present (ie, neutropenia/thrombocytopenia), the investigator will decide whether surgery will proceed according to schedule; a washout period is not needed.

Eligible patients include men and women with histologically confirmed diagnosis of early invasive HER2 negative adenocarcinoma of the breast with germline BRCA1/2 mutations who are suitable for neoadjuvant therapy.

A patient will participate in up to 4 periods: screening, talazoparib treatment phase, safety follow-up, and long-term follow-up. The study schematic is provided in Figure 1.

Patients will be evaluated at screening for the presence of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation. Long term follow-up period is at least 5 years, which starts from the date of surgery for EFS and after first dose of drug for OS. Presence of germline BRCA1/2 mutation will confirmed by a local CLIA (Clinical Laboratory Improvement Amendments) certified test. Germline DNA from blood will also be tested centrally for mutations in BRCA1 and BRCA2 using a BRACAnalysisCDx test (Myriad Genetics), except for those patients who already have evidence of gBRCA1/2 mutation by Myriad BRCAnalysisCDx post 2016.

For all patients, disease status will be assessed at screening by computed tomography (CT) scans (chest, abdomen, pelvis) or magnetic resonance imaging (MRI) for assessment of distant metastases.

For all patients, hematology and serum chemistry samples will be collected every 2 weeks on Cycles 1 and 2 and Day 1 of each cycle for cCycles 3 to 6. Other general and laboratory assessments will be performed at regular intervals throughout the study according to the Schedule of Activities (Table 1).

All patients entered on the trial will receive neoadjuvant talazoparib 1 mg/day PO for 24 weeks, with the exception of patients with baseline moderate renal impairment (as defined by an eGFR ≥30 and <60 mL/min/1.73m^2) who will receive a starting dose of 0.75 mg/day of talazoparib; followed by surgery and assessment of pCR.

For all patients, study drug treatment should continue until completion of protocol assigned therapy, followed by surgery unless the patient is no longer clinically benefitting in the opinion of the investigator, there is unacceptable toxicity, withdrawal of consent, or death. Dosing interruptions are permitted for a period of 28 days to allow recovery from drug related toxicities. Patients who receive less than 80% of the prescribed talazoparib dose during the neoadjuvant treatment period will not be evaluable.

Patients will undergo definitive breast surgery within 6 weeks of the last dose of talazoparib. Tumors must be removed by either lumpectomy or mastectomy with clinically appropriate axillary surgery. Any involved axillary nodes should be marked with a metallic indicator or other standard approach before systemic therapy to ensure their removal at the time of definitive surgery as recommended by FDA guidances.[50] For patients with clinically negative axillary lymph nodes, sentinel lymph node biopsy, using institutional procedures such as dual blue dye or radioisotope tracers, should be performed at the time of definitive surgery and include resection of at least two nodes whenever possible.[15,67] The surgical specimens (breast and axillary lymph node tissue) will be sent to the central lab as soon as possible for evaluation of pCR (defined per protocol) by central Pathologists at M.D. Anderson Cancer Center. Any further post-operative therapy, either local or systemic will be at the discretion of the treating physician. A post-surgical follow up visit will take place after 4 weeks of surgery.

Safety will be assessed by adverse events, physical examinations, vital signs, and clinical laboratory tests. Assessment of abnormal liver tests is described in Section 5.4.3.

Patient reported outcomes will be assessed electronically to evaluate global health status/QoL, functions, and symptoms using the EORTC QLQ C30 and QLQ BR23 questionnaires; CCI [redacted] Additional patient reported outcomes will be assessed electronically to evaluate the proportion of patients with missed expected menstrual period per PRO-CTCAE.

Patient reported outcomes will be assessed electronically during the clinical visit at the following time points: C1D1 (Baseline), C1D15, C2D1, C2D15, D1 of C3-C6, End of Treatment and Follow-up.

An electronic patient reported-antiemesis medication log will be used to record antiemesis medication taken by the patients for 7 consecutive days prior to each clinical visit.

Subjects who progress while on talazoparib will automatically be considered non-responders to talazoparib and will proceed to the standard of care therapy of the treating physician's choice or proceed to surgery if the treating physician feels that is in the patient's best interest. Safety follow-up will occur approximately 28 days after the last dose of study drug or before initiation of a new investigational therapy, whichever occurs first. There will also be an additional post-surgical safety follow up, 4 weeks after surgery, for assessment of wound healing. Long term follow-up will begin after surgery for EFS and after first dose of talazoparib for OS and will take place every 12 weeks thereafter until death, withdrawal of consent for follow up, or study termination by the Sponsor.

Plasma PK samples for determination of talazoparib concentrations will be collected at defined timepoints to describe the steady-state PK of talazoparib in patients with gBRCA mutation-positive HER2 negative breast cancer and to support exploratory analyses to correlate talazoparib exposure and tumor response (eg, pCR, EFS, etc.) and/or select safety findings.

4. PATIENT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Presence of germline BRCA1/2 mutation as confirmed by a local CLIA (Clinical Laboratory Improvement Amendments) certified test. Consent to a blood sample for genomic assessment by the BRACAnalysisCDx test at Myriad Genetics, except for patients who already have evidence of BRCA1/2 mutation by Myriad BRACAnlaysisCDx post 2016.

2. Patients must be willing and able to provide evidence of a personally signed and dated informed consent document indicating that they (or a legally acceptable representative) have been informed of all pertinent aspects of the study.

3. Women and men at least 18 years of age or older.

4. Documentation of histologically confirmed invasive adenocarcinoma of the breast.

5. HER2 negative breast cancer:

   - HER2 negative or non-amplified as determined by the current American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) criteria which are as follows: HER2 testing by IHC as 0 or 1+. If HER2 is 2+, ISH (in situ hybridization) must be performed. HER2 is positive for gene amplification if: IHC 3+ based on circumferential membrane staining that is complete, intense, ISH positive based on: Single-probe average HER2 copy number >/= 6.0 signals/cell Dual-probe HER2/chromosome 17 polysomy (CEP17) ratio >/= 2.0;c,e with an average HER2 copy number >/=4.0 signals/cell Dual-probe HER2/CEP17 ratio >/= 2.0;c,e with an average HER2 copy number <4.0 signals/cell Dual-probe HER2/CEP17 ratio < 2.0;c,e with an average HER2 copy number >/= 6.0 signals/cell.

6. Tumor ≥ T1, N0-3.

7. No evidence of distant metastasis.

8. Adequate bone marrow, hepatic, and renal function as defined by the following:

   - Absolute neutrophil count (ANC) ≥1,500/mm^3 (1.5 x 109 /L);

   - Platelets ≥100,000/mm^3 (100 x 109 /L);

   - Hemoglobin (Hb) ≥9 g/dL (may not have received growth factors or blood transfusions within 14 days before obtaining the hematology values at screening);

- GFR ≥30 mL/min/1.73 m^2 by the modification of diet in renal disease [MDRD] calculation [available via www.mdrd.com];
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5X ULN;
- Total serum bilirubin <1.5X ULN.

9. ECOG performance status 0 or 1.

CCI [redacted]

11. Women of childbearing potential (WCBP) must have a negative serum or urine pregnancy test within 14 days prior to enrollment. WCBP must be using a highly effective method of contraception to avoid pregnancy throughout the study and for 7 months after the last dose of investigational product (IP). Male patients with female partners of reproductive potential and pregnant partners must use a condom (even after vasectomy) during treatment with talazoparib and for 4 months after the final dose.

12. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

13. Female patients of non-childbearing potential must meet at least 1 of the following criteria:

    a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

    b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    c. Have medically confirmed ovarian failure;

    d. All other female patients (including female subjects with tubal ligations) are considered to be of childbearing potential.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

2. Participation in other studies involving investigational drug(s) within 12 months prior to study entry and/or during study participation.

3. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4. Any other previous antitumor therapies for the current cancer event. Treatment for ductal carcinoma in situ (DCIS) is allowed; ie, surgery, hormonal therapy and radiation.

5. Evidence of distant metastasis apparent prior to randomization.

6. Patients with inflammatory breast carcinoma.

7. Malignancy within the last 3 years, except:

   - Stage 1 melanoma which does not require any further treatment after adequate surgical excision;
   - Adequately treated non-melanoma skin cancer;
   - Curatively treated in situ cancer of the cervix;
   - Stage 1, Grade 1 endometrial carcinoma; or
   - Adequately treated contralateral breast carcinoma which has been disease free for a year;
   - Other solid tumors including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years.

8. Concomitant use strong of P-gp inhibitors or inducers or BCRP inhibitors (see Section 5.7).

9. Previous or concomitant systemic anti-cancer therapies used for the treatment of cancer in the last 3 years.

10. Prior treatment with a PARP inhibitor in any disease setting.

11. Pregnant female subjects, breastfeeding female subjects, fertile male subjects, and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 7 months for females, 4 months for males after the last dose of investigational product.

12. Major surgery within 14 days prior to study entry; patients must have recovered from any effects of any major surgery.

13. No known history of cardiovascular disease, including any of the following:

    - Myocardial infarction or symptomatic cardiac ischemia within 24 weeks before screening;

    - Congestive heart failure New York Heart Association Class III or IV;

    - History of clinically significant ventricular arrhythmias eg, history of sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes) within one year prior to randomization;

    - History of Mobitz II second degree or third-degree heart block, unless a permanent pacemaker is in place;

    - Hypotension as indicated by systolic blood pressure <86 mm Hg (millimeters of mercury) at screening;

    - Bradycardia as indicated by heart rate (HR) <45 beats per minute on the screening electrocardiogram (ECG);

    - Uncontrolled hypertension as indicated by systolic blood pressure >170 mm Hg or diastolic blood pressure >105 mm Hg at screening. However, patients can be re-screened after adequate control of blood pressure is achieved.

14. Active clinically significant infection either Grade >2 by NCI-CTCAE v4.03, or requiring the use of parenteral anti-microbial agents within 14 days before day 1 of study drug.

15. Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorders.

16. Non-healing wound, ulcer or bone fracture.

17. Known hypersensitivity to any of the components of talazoparib.

18. Patients with myelodysplastic syndrome/acute myeloid leukemia.

19. Patients with uncontrolled seizures.

20. Any evidence of other disease or any concomitant medical or psychiatric problems which in the opinion of the Investigator would prevent completion of treatment or follow-up, such as:

    - Evidence of severe or uncontrolled cardiac disease, uncontrolled ventricular arrhythmia, myocardial infarction within 12 months prior to study entry, or active infection including hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV);

    - Patients unable to swallow orally administered medication, or patients with gastrointestinal disorders likely to interfere with absorption of the trial medication.

4.3. Lifestyle Requirements

4.3.1. Contraception

In this study, fertile male patients and female patients who are of childbearing potential as applicable to the study will receive talazoparib, which has been associated with teratogenicity/fetotoxicity in preclinical studies. Talazoparib is clastogenic in nonclinical genetic toxicological evaluations. Talazoparib also caused fetal malformations, structural variations, and death in an embryo fetal development study in rats.

Patients who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a of highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 7 or 4 months for females and males, respectively, after the last dose of IP. The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected a highly effective method of contraception for the individual patient (and his or her partner) from the permitted list of contraception methods (see below) and will confirm that the patient has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the patient of the need to use a highly effective method of contraception consistently and correctly and document the conversation and the subject's affirmation in the patient's chart. In addition, the investigator or designee will instruct the patient to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the patient or the partner. Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use).

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of IP and continuing for at least 4 months after the last dose of talazoparib. Contraception should be considered for a nonpregnant female partner of childbearing potential.

4.3.2. Women of Childbearing Potential (WCBP) Definition

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;

    - Documented bilateral salpingectomy;

    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above conditions can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the patient's medical record for the study.

3. Postmenopausal female.

A postmenopausal state is defined as age 60 or older or no menses for 12 months without an alternative medical cause.

A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).

Females on HRT and whose menopausal status is in doubt will be required to use one 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.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the team SharePoint site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and IP identifiers, patient study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Council for Harmonisation (ICH) guidelines, IP is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 [ICH E6 1.33]). For this study, the IP is talazoparib.

5.1. Allocation to Treatment

Allocation of patients to treatment groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, randomization number (although non-randomized, a randomization number is still required for all patients to reconcile and merge separated data files), and the patient number. The site personnel will then be provided with a treatment assignment and dispensable unit (DU) or container number when IP is being supplied via the IRT system. The IRT system will provide a confirmation report containing the patient number and DU or container number assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

5.2. Patient Compliance

For self-administration of talazoparib at home, compliance will be captured and completed by the patient using an electronic diary. Patients will record the daily administration of the study drug (talazoparib). Data entered in the diary will be compared with drug accountability done at the site prior to dispensing additional study drug. In the event of unexplained discrepancies, drug accountability data will prevail in determining patients' degree of compliance, which will be recorded in the case report form (CRF). Patients will be considered out of compliance if >20% of monthly doses are missed.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

Talazoparib drug product will be supplied as 2 clinical dosage strengths of 0.25 mg or 1 mg, calculated relative to the talazoparib free base, for oral administration. Depending on the prescribed dose, patients may take two 0.25 mg capsules for the 0.5 mg dose, or three 0.25 mg capsules for the 0.75 mg dose. The drug substance is a 4 methylbenzenesulfonate (tosylate) salt of talazoparib free base, the active moiety. The drug product consists of talazoparib tosylate drug substance formulated with silicified microcrystalline cellulose (SMCC) filled into hydroxypropyl methylcellulose (HPMC) as immediate release capsules. The drug product should be stored at room temperature (15 to 30°C; 59 to 86°F). The capsules are supplied in induction-sealed high-density polyethylene (HDPE) bottles.

5.3.2. Preparation and Dispensing

Talazoparib will be dispensed using an Interactive Web Response System (IWRS) drug management system every 4 weeks through week 24. A qualified staff member will dispense the IP via unique container numbers in bottle(s) provided, in quantities appropriate for the study visit schedule. The patient/caregiver should be instructed to maintain the product in the bottle(s) provided throughout the course of dosing and return the bottle to the site at the next study visit.

5.4. Administration

Talazoparib will be self-administered by mouth at approximately the same time each day outside the clinic, except on days when PK is assessed; patients will withhold their dose until after the pre-dose PK blood sample is drawn. Talazoparib can be administered with or without food. Patients will swallow the IP whole, and will not manipulate or chew the IP prior to swallowing. Patients should not make up missed or vomited doses; dosing should resume on the next calendar day unless otherwise instructed.

Daily dosing of talazoparib can be interrupted for recovery from toxicity for up to 28 days. Thereafter, treatment at the same or a reduced dose can be considered based on a discussion between sponsor or designee and Investigator if the patient has not developed progressive disease. Dose modifications should be made based on observed toxicity as follows:

- Grade 1 or 2 toxicity: No requirement for dosing interruption or dose reduction. If the toxicity persists at grade 2, a dose reduction to the next lower dose level (eg, from 1 mg/day to 0.75 mg/day) may be implemented at the discretion of the Investigator;

- Grade 3 toxicity: Daily dosing should be stopped. Talazoparib dosing may resume at the next lower dose level (eg, from 1 mg/day to 0.75 mg/day, 0.75 mg/day to 0.5 mg/day);

- Grade 4 toxicity: Daily dosing should be stopped. Talazoparib may resume at a lower dose level (1-2 dose level decrease) with the approval of the medical monitor when toxicity resolves to grade 1 or returns to baseline. See the following table (Table 3) for further details. Also, refer to Section 5.4.1 and Table 4, Dose Modifications for Talazoparib Due to Adverse Events.

Table 3. Dose Modifications for Talazoparib Toxicities

	Dose Level
Initial dose level	1 mg/day[a]
First dose level reduction	0.75 mg/day
Second dose level reduction	0.5 mg/day

[a.] Patients with baseline moderate renal impairment will have a starting dose of 0.75 mg/day.

Talazoparib will be permanently discontinued for individual patients as a result of any unresolved Grade 3 or Grade 4 toxicity or based on a decision by the patient or Investigator that continued treatment is not in the patient's best interest. Talazoparib must be permanently discontinued for unresolved Grade 3 toxicity lasting longer than 14 days or for Grade 4 toxicity lasting longer than 3 days.

5.4.1. Dose Modifications for Talazoparib Due to Adverse Events

The daily dose of talazoparib may be reduced sequentially in 0.25 mg per day increments depending on the degree of toxicity. Dose modifications for talazoparib due to adverse events are described in Table 4. Patients will receive a starting dose of 1 mg/day of talazoparib, with the exception of patients with baseline moderate renal impairment (as defined by an eGFR ≥30 and <60 mL/min/1.73 m^2) who will receive a starting dose of 0.75 mg/day of talazoparib.

Table 4. Dose Modification of Talazoparib Due to Adverse Events

Toxicity	Management of Adverse Events
Grade 1 or 2	**No requirement for dosing interruption or dose reduction**
Selected hematologic grade 3 or 4 events	
Anemia (hemoglobin <8.0 g/dL)	Hold talazoparib and implement supportive care as per local guidelines. Monitor weekly until hemoglobin returns to 9.0 g/dL or better, then resume talazoparib at a reduced dose at the initiation of the next cycle. Talazoparib may be reduced by 1 dose level as described in Section 5.4. If anemia with hgb <8.0 g/dL recurs after dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until hemoglobin returns to 9.0 g/dL (Day 1), then resume talazoparib at a further reduced dose at the initiation of the next cycle. If anemia persists for >4 weeks without recovery of hemoglobin to at least 9.0 g/dL despite supportive care measures at any dose level, discontinue talazoparib and consider referral to a hematologist. Transfusions and other supportive measures are permitted to support management of hematological toxicities at any occurrence.
Neutropenia (ANC <1000/μL)	Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC ≥1500/μL, then resume talazoparib at a reduced dose at the initiation of the next cycle. If neutropenia recurs after the dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC ≥1500/μL, then resume talazoparib at a further reduced dose at the initiation of the next cycle. If neutropenia persists for >4 weeks without recovery to ≥1500/μL at any dose level despite supportive care measures, discontinue talazoparib and consider a referral to a hematologist. G-CSF and GM-CSF may be used at investigators discretion for the supportive (including prophylactic) treatment of neutropenia at any occurence.
Thrombocytopenia (platelets <50,000/μL)	Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets ≥50,000/μL, then resume talazoparib at a reduced dose at the initiation of the next cycle. If thrombocytopenia (<50,000/μL) recurs after one dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets ≥75,000/μL, then resume talazoparib a further reduced dose at the initiation of the next cycle. If thrombocytopenia persists for >4 weeks without recovery to ≥50,000/μL despite supportive care measures, discontinue talazoparib and consider a referral to a hematologist. Thrombopoietin analogues and/or platelet transfusions may be used at investigators discretion for the supportive treatment of thrombocytopenia at any occurrence.
Nonhematologic laboratory Grade ≥3 events, except abnormal liver tests	Hold talazoparib as follows: For Grade 3 laboratory abnormalities, hold talazoparib until the laboratory abnormality resolves to Grade ≤2 (to baseline grade for creatinine increases). Resume talazoparib at the same dose or reduce of one dose level at the initiation of the next cycle.

Toxicity	Management of Adverse Events
	If Grade 3 laboratory abnormality recurs, hold talazoparib until the laboratory abnormality resolves to Grade ≤2 (to baseline grade for creatinine increases). Reduce talazoparib of one dose level if the dose was not previously reduced, or to further reduced dose level if subject was previously dose reduced at the initiation of the next cycle. For Grade 4 laboratory abnormalities, hold talazoparib until the laboratory abnormality resolves to Grade ≤2 (to baseline grade for creatinine increases). Reduce talazoparib of one dose level at the initiation of the next cycle. Talazoparib must be discontinued if a Grade 4 adverse event recurs after treatment resumes. Implement supportive care per local guidelines. Contact medical monitor to discuss potential dose modification. Talazoparib must be permanently discontinued for unresolved Grade 3 toxicity lasting longer than 14 days or for Grade 4 toxicity lasting longer than 3 days. Treatment may be resumed at a 1 dose level reduction if clear clinical benefit is observed, after discussion with the Sponsor.
Grade ≥3 abnormal liver tests	Hold talazoparib for liver test abnormalities as specified in Section 5.4.3. Guidelines for follow-up for possible drug-induced liver injury and for resuming talazoparib after the liver test abnormalities resolve to baseline grade are provided in Section 5.4.3. The criteria for permanent discontinuation talazoparib/placebo are provided in Section 5.4.3.
Nonlaboratory Grade ≥3 events	Hold talazoparib as follows: For Grade 3 adverse events, hold talazoparib until the adverse event resolves to Grade ≤1 or baseline. Resume talazoparib at the same dose or reduce by 1 dose level as described in Section 5.4. For Grade 4 adverse events, permanently discontinue talazoparib. Implement supportive care per local guidelines. Contact medical monitor to discuss potential dose modification. Talazoparib must be permanently discontinued for unresolved Grade 3 toxicity lasting longer than 14 days. Treatment may be resumed at a 1 dose level reduction if clear clinical benefit is observed, after discussion with the medical monitor. Talazoparib must be discontinued if a grade 4 adverse event recurs after treatment resumes.

ANC=absolute neutrophil count.

5.4.2. Talazoparib Dose Re-Escalation

Dose re-escalation of talazoparib is not allowed.

5.4.3. Modifications Due to Abnormal Liver Tests (All Treatments)

Patients who develop abnormal liver tests (aspartate aminotransferase [AST], alanine aminotransferase, [ALT], total bilirubin [TBili]), abnormal international normalized ratio (INR) values, or signs or symptoms consistent with hepatitis during study treatment may meet the criteria for temporarily withholding or permanently discontinuing study drug.

Patients who have abnormal liver tests or meet the criteria for permanent discontinuation or temporary withholding of study drug will be followed up according to the recommendations in this section.

Study drug should be withheld for any liver test abnormality listed in Table 6. When withholding study drug, follow-up should continue for possible drug-induced liver injury (Table 5) until the liver test abnormalities resolve to baseline grade. However, talazoparib should be permanently discontinued if any liver test elevation persists for more than 7 days.

Table 5. Criteria for Temporary Withholding of Study Drug in Association With Liver Test Abnormalities

Screening AST or ALT Value	Elevation[a]
≤3 × ULN	>5 × ULN (ALT or AST ≥3 × ULN with the presence of signs and symptoms consistent with acute hepatitis and/or eosinophilia [≥500 eosinophils/µL])
>3 × ULN and ≤5 × ULN	>8 × ULN
Baseline Total Bilirubin Value	
≤1.5 × ULN	>3 × ULN
>1.5 × ULN and ≤3 × ULN (Patients with Gilbert syndrome or for whom indirect bilirubin concentrations suggest an extrahepatic source of elevation)	>5 × ULN

For re-challenge, dose modification may be required per Table 3.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
a. Talazoparib should be permanently discontinued if any elevation persists for more than 7 days.

Re-challenge with talazoparib following liver test abnormalities is not permitted if these abnormalities are accompanied with signs or symptoms consistent with drug-induced liver toxicity or meet permanent discontinuation criteria. Re-challenge with talazoparib may be considered at a 0.25 mg/day reduction if an alternative cause for the abnormal liver tests (ALT, AST, TBili) is discovered and the laboratory abnormalities resolve to normal or baseline values. The investigator and sponsor should discuss and agree with any decision to rechallenge any of the assigned study drugs. Following re-challenge, patients should be closely monitored for signs and symptoms of hepatitis and/or abnormal liver test results. Study drug treatment should be permanently discontinued permanently if any of the following criteria are met:

- Patients with AST/ALT and TBili baseline values within the normal range who subsequently present with AST **OR** ALT values >3 × ULN **AND** a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available (Note: in the presence of elevated alkaline phosphatase associated with bone metastases, gamma glutamyl transferase [GGT] should be tested and the results should be within the reference range);

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller);

  - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

- Patients with AST/ALT >5 × ULN that persists for more than 7 days (AST/ALT >8 × ULN for patients with hepatic involvement);

- Patients with AST/ALT >20 × ULN that persists for longer than 3 days;

- Patients with TBili >3 × ULN that persists for longer than 7 days (>5 × ULN for patients with Gilbert's disease);

- No alternative cause explains the combination of the above laboratory abnormalities.

When study drug treatment is temporarily withheld or permanently discontinued due to a potential drug induced liver injury, a period of close observation is to commence until the liver test abnormalities return to baseline or normal values. The evaluations listed in Table 6 should be performed.

Table 6. Monitoring of Liver Tests for Potential Drug Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]) and INR Tests
After the initial liver test abnormality	Within 24 hours
If AST or ALT ≥3 × ULN (>5 × ULN if baseline ALT/AST is >3 × ULN), and total bilirubin >2 × ULN or INR >1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥3 × ULN (>5 × ULN if baseline ALT/AST is >3 × ULN) and total bilirubin or INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; ULN = upper limit of normal.

As drug-induced liver injury is a diagnosis of exclusion, it is important to initiate investigation of alternative causes for abnormal liver tests, which may include consultation with a hepatologist. Contact the medical monitor with questions regarding sufficient follow-up tests.

5.5. Investigational Product Storage and Handling

The investigator or an approved representative, eg, pharmacist, will ensure that talazoparib is stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Talazoparib is considered a cytotoxic and clastogenic agent; precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including personal protective clothing, disposable gloves, and equipment. Patients should be advised that oral anticancer agents (ie, talazoparib) are toxic substances and that other caregivers should always use gloves when handling the capsules.

IPs should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the talazoparib SRSD will be superseded by the storage conditions stated on the label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of IP receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the IP must be quarantined and not used until Pfizer provides permission to use the IP. It will not be considered a protocol deviation if Pfizer approves the use of the IP after the temperature excursion. Use of the IP prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct patients on the proper storage requirements for take home IPs.

Refer to the IP Manual for additional guidance on storage conditions and actions to be taken when conditions are outside of the pre-specified range.

5.6. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the IP supplies. All IP will be accounted for using a drug accountability form/record. All bottles of study drug must be returned to the investigator by the patient at every visit and at the end-of-treatment visit. Patients who do not return bottles at the end-of-treatment visit will be reminded to bring them at their next visit.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused IP (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.7. Concomitant Treatment(s)

Patients must be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with the investigator. Any medications including herbal supplements, vitamins, or treatment taken by the patient from 28 days prior to the start of study treatment and up to 28 days following the last dose of IP, including the start and end dates of treatment and the reason for their administration, must be recorded on the CRF.

Use of the following treatments is prohibited prior to study entry (28 days prior to randomization), during the study, and for 30 days following the last dose of the IP, or as otherwise noted.

- Prior or concurrent treatment with another PARP inhibitor.
- Previous or concomitant systemic anti-cancer agents used for the treatment of cancer in the last 3 years.
- Use of the following P-gp inhibitors (amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, verapamil, and valspodar), P-gp inducers (avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort) or BCRP inhibitors (curcumin, cyclosporine, elacridar [GF120918], and eltrombopag) is prohibited.

- While the following mediations are not prohibited from use during study conduct, caution should be used upon concomitant use of the following transporter inhibitors with talazoparib: atorvastatin, azithromycin, conivaptan, diltiazem, diosmin, eliglustat, felodipine, flibanserin, fluvoxamine, piperine, quercetin, and schisandra chinensis extract.

The start date, stop date, and indication for concomitant treatments and/or therapies and medications received from screening until end of treatment will be recorded on the CRF.

6. STUDY PROCEDURES

6.1. Screening

See Table 1 for screening procedures. Screening for gBRCA1/2 Mutations:

- If positive gBRCA1/2 status has been confirmed by a local CLIA certified test, patients may enroll and commence study treatment, provided all other inclusion/exclusion criteria are met and screening tests have been satisfactorily completed.

- A blood sample must be sent to Myriad Genetics for central testing (BRACAnalysisCDx test), except for those patients who already have evidence of gBRCA1/2 mutation by Myriad BRACAnalysisCDx post 2016.

- In the event of discrepant results, where the local BRCA test is positive for gBRCA1/2 mutation and the central Myriad BRACAnalysis test is negative, the decision on further trial continuation will be decided by the investigator and discussed with the sponsor based on a risk-benefit evaluation.

6.2. Treatment Period

See Table 1 for treatment procedures.

6.3. Safety Follow-up

For safety follow-up procedures after the treatment period, see Table 1. Safety follow-up will occur a minimum of 28 calendar days after the last dose of study drug or before initiation of a new antineoplastic therapy (whichever occurs first) to capture any potential AEs (see the Time Period for Collecting Adverse Event/Serious Adverse Event Information section). Contact with the patient for AE follow-up may be done via phone call if the patient does not come to the site. There will be an additional post-surgical follow up 4 weeks after surgery.

6.4. Long Term Follow-up

For long-term follow-up procedures after the treatment period, see Table 1. This period begins after surgery for EFS and after first dose of talazoparib for OS. Survival status can be obtained by any means including telephone, during a visit, chart review, or contact with someone who is knowledgeable of the patient's survival status (eg, relative, friend, referring

healthcare provider). If allowed by local laws and regulations, survival status may be obtained from public records for patients withdrawing consent from the study or for patients lost to follow-up.

6.5. Patient Withdrawal

Withdrawal of consent:

Patients who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Patients should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of IP or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the patient after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the patient remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the patient's medical records.

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal from the Study Due to Adverse Events (see also the Patient Withdrawal section) or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. This includes follow-up with persons authorized by the patient. "Lost to follow-up" is defined by the inability to reach the patient after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the patient to 1 registered mail letter. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record and CRF. If it is determined that the patient has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the patient remains lost to follow-up, then the contact date should be reported and documented in the patient's medical records and CRF.

In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any AEs.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor. Patients will be enrolled to account for a 10% drop-off rate.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

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7.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test (urine pregnancy tests must have a sensitivity of at least 25 mIU/mL for human chorionic gonadotropin) will be performed as per the SOA.

A negative pregnancy test result is required before the patient may receive talazoparib. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/(ECs) or if required by local regulations.

Serum or urine pregnancy tests will be conducted with the test kit provided by the central laboratory in accordance with instructions provided in its package insert. Patients who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory). In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of IP and from the study.

7.2. Companion Diagnostics for Eligibility

Patients are required to have HER2 negative breast cancer that is gBRCA positive. The blood samples will be sent to central lab for analysis with results returned within 2 weeks.

BRCA testing can be performed using a local, CLIA certified blood test. If local test is done (other than Myriad BRACAnalysisCDx post 2016), an additional sample will need to be sent for central testing to MYRIAD genetics. Patients must also consent to a blood sample for central genomic assessment using the BRACAnalysisCDx test by Myriad Genetics, except for patients who already have evidence of BRCA1/2 mutation by MYRIAD BRCAnalysisCDx post 2016.

7.3. Efficacy Assessments

7.3.1. Primary Efficacy Endpoint: Pathological Complete Response

The primary efficacy endpoint is the pathologic complete response to talazoparib after 24 weeks of neoadjuvant therapy followed by surgery. pCR will be assessed by histological examination of the post-surgical specimen by ICR. The post-surgical specimen should be sent to the central lab as soon as possible. Further details can be found in the laboratory manual.

7.3.2. Assessment of Secondary Efficacy Endpoints

The secondary endpoints include pCR by investigator, RCB, pCR (in breast), EFS at 3 years and OS at 3 years.

The study assessments of efficacy for these endpoints (RCB by ICR and pCR by investigator) will be assessed by histological examination of the post-surgical specimen. EFS and OS will be collected by telephone follow up of patients every 12 weeks during the long term follow up period. Follow up for EFS will start from date of surgery. Follow up for OS will start from day of first dose of talazoparib.

7.4. Patient Reported Outcomes Assessments

Global health status/quality of life, functioning, and symptoms data will be collected electronically using the EORTC QLQ-C30 and QLQ BR23 questionnaires.

The EORTC QLQ-C30 is a standardized instrument that assesses cancer-specific patient-reported global quality of life, functioning, and disease/treatment-related symptoms. Patients will self-rate their self-care, activity level, pain/discomfort, and mental health during the past week by choosing 1 of 4 possible responses that record the level of intensity (not at all, a little, quite a bit, and very much) within each dimension. The questionnaire also asks the patient to rate their overall health and overall quality of life within the past week on a scale of 1 to 7, where 1 is “very poor” and 7 is “excellent.” The QLQ-C30 questionnaire is provided in Appendix 2.

The EORTC QLQ-BR23 (Breast Cancer Quality of Life Questionnaire) is a breast cancer-specific module of the EORTC questionnaire that assesses the functioning and symptoms of patients with breast cancer. The EORTC QLQ-BR23 functional scales consist of the 4 scales that assess body image, sexual functioning, sexual enjoyment, and future perspective. The EORTC QLQ-BR23 symptom scales consist of the 4 scales that assess systemic therapy side effects, breast symptoms, arm symptoms, and upset by hair loss. Patients will choose 1 of 4 possible responses that record level of intensity (not at all, a little, quite a bit, very much) within each dimension. The QLQ-BR23 module is provided in Appendix 3.

For the global health status/QoL, functional and symptom scores in EORTC QLQ-C30 and QLQ-BR23, a ≥10 point change from baseline will be used to indicate clinically meaningful change.[68]

Missed expected menstrual period will be assessed electronically using the PRO-CTCAE questionnaire, a patient-reported outcome measure developed to evaluate symptomatic toxicity in patients on cancer clinical trials. The PRO-CTCAE questionnaire is provided in Appendix 5. There are no guidelines yet established by the US National Cancer Institute (developer of PRO-CTAE) for how best to analyse PRO-CTCAE data longitudinally.[69] Results from PRO-CTAE will be reported descriptively.

On Day 1, patients will complete these questionnaires before the first dose of study drug. At subsequent visits, patients will complete these questionnaires at the site before any other study activities and in the same order at each visit. These questionnaires will be collected according to the schedule of assessments in Table 1.

7.5. Pharmacokinetic Assessments

Plasma PK samples for determination of talazoparib concentrations will be collected prior to dosing (pre-dose) on Day 1 of Cycles 2, 3, and 4. Patients must be instructed to withhold their daily dose of talazoparib on PK sampling days until the pre-dose PK sample and safety assessments (ie, hematology, blood chemistry, and ECGs) have been completed. The date and exact time of the PK sample collection and the most recent talazoparib dosing times (before and after PK sample collection) will be recorded on the CRF. The date of any missing dose(s) should also be recorded in the CRF.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, pre-dose samples on Day 1 of Cycles 2, 3 and 4 will not be captured as a protocol deviation, as long as the PK sample is collected prior to talazoparib administration on that calendar day and the exact time of the PK sample collection and the exact dosing time are noted on the source document and data collection tool (eg, CRF).

One 4 mL sample of venous blood will be collected in appropriately labeled lavender top K_3 EDTA collection tubes at the protocol-specified times. Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

Blood samples will be collected from all participating patients for PK assessments of talazoparib on Day 1 of Cycles 2, 3, and 4 before administration of the talazoparib dose on that day. In the event a pre-dose sample cannot be/is not collected as scheduled, every effort should be made to collect a makeup pre-dose sample on Day 1 of a later cycle beyond

Cycle 4 following the same rules described. Documented rationale is needed in the database for any missing and delayed sampling.

Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation.

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Refer to the Study Laboratory Manual for detailed collection, processing and shipping procedures.

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7.8. Rater Qualifications

Radiologists will be board-certified in their discipline or carry similar credentials as outlined in the Independent Radiographic Review Charter.

7.9. Safety Assessments

Safety endpoints include adverse events (graded according to the NCI CTCAE, version 4.0), physical examination (including blood pressure and pulse rate), and laboratory tests (hematology and chemistry).

7.9.1. Adverse Events

The procedures for the investigator assessment of adverse events are presented in Section 8.

7.9.2. Physical Examinations

Physical examinations will be conducted according to the Schedule of Activities. At screening, this will constitute an assessment of systems (eg, general appearance, head, eyes, ears, nose, mouth, throat, skin, heart, lung, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal). During treatment, systems will be assessed per standard of care at the study site or as clinically indicated by symptoms. A clinical exam of breast and axilla should be included in each physical exam. If the patient has evidence of clinical disease progression, treatment on study should be discontinued. These patients should either switch to alternate systemic therapy or go straight to surgery so as not to preclude potentially curative surgery.

7.9.3. Vital Signs

Vital sign measurements (blood pressure, heart rate, and temperature) and weight will be assessed as shown in the Schedule of Activities. Height will also be measured at screening.

7.9.4. Clinical Laboratory Assessments

Blood samples for hematology and serum chemistry assessments will be collected as shown in Table 1 and analyzed at a central laboratory. In addition to (but not in place of) these central laboratory assessments, the Investigator may also collect local laboratory assessments within 3 days prior to a scheduled visit to guide decision-making at regularly scheduled visits. The required laboratory tests are listed in Table 7.

Table 7. Required Laboratory Tests

Hematology	Serum Chemistry	Urinalysis (dipstick)	Additional tests
Hematocrit	Albumin	Color clarity Specific gravity pH Protein Glucose Ketones Bilirubin urobilin Blood Nitrite Leukocyte esterase Microscopy Cellular elements- RBC	CCI [redacted]
Hemoglobin	Total protein		
Mean corpuscular volume	Alkaline phosphatase		
RBC	ALT		
Platelets	AST		
	Total bilirubin[a]		
WBC with differential	BUN		
• ANC	Creatinine		
• Lymphocytes	Glucose (non-fasting)		
• Monocytes	Bicarbonate		
• Eosinophils	Calcium		
• Basophils	Chloride		
	Magnesium		
	Phosphate		
	Potassium		
	Sodium		
	LDH		

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRF = case report form; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell.
The laboratory manual for this study provides details regarding sample collection procedures, laboratory tests, and additional tests that may be required.

a. For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, PT/INR, and alkaline phosphatase.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) serious adverse events (SAEs) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the IP under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the IP under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy (EDP), exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of suspected causal relationship to the IP(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an IP under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient /legally acceptable representative. In addition, each study subject/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Patient Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a patient withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting Adverse Event/Serious Adverse Event Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the subject provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving IP), through and including a minimum of 28 calendar days after the last administration of the IP.

For patients who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting Serious Adverse Events to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to IP must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

8.1.4.2. Recording Non-serious Adverse Events and Serious Adverse Events on the Case Report Form

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the IP caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the IP caused the event, then the event will be handled as "related to IP" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to IP, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- EDP;
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Secondary primary malignancies should be reported as an SAE. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed below.

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Patients who experience a transaminase elevation above 3 times the ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patient’s individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For patients with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor.

The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, GGT, PT/INR, total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product during Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the IP under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.4. Exposure during Pregnancy

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the IP; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the IP. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products);

- A male has been exposed (eg, because of treatment or environmental exposure) to the IP prior to or around the time of conception and/or is exposed during his partner's pregnancy;

- If a patient or patient's partner becomes or is found to be pregnant during the subject's treatment with the IP, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the IP;

- Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.4.1. Exposure during Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.4.2. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.5. Medication Errors and Lack of Efficacy

Other exposures to the IP under study may occur in clinical trial settings, such as medication errors and lack of efficacy.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors and lack of efficacy*	All (regardless of whether associated with an AE)	Only if associated with an SAE

*For lack of efficacy (particularly for studies conducted with vaccines, contraceptives, and products used in the treatment of life-threatening diseases or conditions [eg, anti-infectives]), see the Lack of Efficacy section below.

8.5.1. Medication Errors

Medication errors may result from the administration or consumption of the IP by the wrong patient, or at the wrong time, or at the wrong dosage strength. Medication errors include:

- Medication errors involving patient exposure to the IP;

- Lack of dose reduction as specified by the protocol;
- Continuation of treatment after patient met disconintuation criteria;
- Incorrect study drug dose (overdose or underdose) taken by patient;
- Patient did not take study medication for 6 or more days within 4 weeks, unless dose was withheld due to an AE;
- Patient did not receive treatment as assigned by IRT;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Such medication errors occurring to a study patient are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.5.2. Overdose

An overdose of talazoparib is defined as any dose over the prescribed dose; there is no specific treatment in the event of an overdose, and symptoms are not established. In the event of overdose, treatment with talazoparib should be stopped, and physicians should both consider gastric decontamination and follow general supportive measures. All overdose events are to be reported within 24 hours of awareness (as per the requirements dictated in Section 8.5.1, Medication Errors) by the study site whether or not the overdose is associated with an adverse event and the sponsor/medical monitor must be contacted. Whether or not the overdose is accompanied by an AE, as determined by the investigator, the overdose is recorded on the adverse event page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are also recorded on an AE page of the CRF. Overdose should also be reported to Pfizer Safety within 24 hours on a Common Terminology for Serious Adverse Events (CTSAE) Report Form.

8.5.3. Lack of Efficacy

Lack of efficacy in an approved indication should be reported as an SAE to Pfizer Safety.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is described in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

Two analyses are planned, including an interim and a final analysis. The interim analysis will be performed to evaluate the safety as well as the primary endpoint (pCR) after 28 evaluable patients receive talazoparib 1 mg QD for 24 weeks, followed by surgery and central assessment of pCR. The final analysis of the primary endpoint will be performed when the last patient enrolled who does not discontinue treatment prematurely completes talazoparib treatment 1 mg QD for 24 weeks, followed by surgery and central assessment of pCR, withdraws consent, discontinues from the study, or dies, whichever occurs first.

Statistical Methods

Analysis populations:

Evaluable population is the primary analysis population for all efficacy endpoints at the interim analysis as well as the final analysis and is defined as all patients enrolled in the study who receive 24 weeks of talazoparib treatment 1 mg QD, undergo breast surgery and central pCR assessment or who otherwise progress or die prior to being evaluated for pCR. All efficacy analyses will be conducted in the evaluable population unless otherwise specified in the statistical analysis plan.

For all patients, study drug treatment should continue until completion of protocol assigned therapy, followed by surgery unless the patient is no longer clinically benefitting in the opinion of the investigator, there is unacceptable toxicity, withdrawal of consent, or death. Dosing interruptions are permitted for a period of 28 days (one period up to 28 days OR several interruptions that total a number of days <80% of the prescribed course of treatment of 24 weeks) to allow recovery from drug related toxicities. Patients who receive less than 80% of the prescribed talazoparib dose during the neoadjuvant treatment period will not be part of the evaluable population. However, patients who progress or die before pCR can be assessed (regardless of whether or not they received 80% of study treatment) by investigator and by ICR will be considered non-responders in the evaluable population.

The intent to treat (ITT) analysis and safety populations are defined as all patients enrolled in the study who received at least one dose of talazoparib. All efficacy analyses will also be reported in the ITT analysis population, unless otherwise specified. All safety analyses will be reported using the safety population. Drug exposure in the safety analysis population will be summarized using descriptive statistics.

PRO analysis population is defined as all patients who completed a baseline and at least one post baseline quality-of-life assessment prior to the end of study treatment.

The PK analysis population is defined as all patients treated with talazoparib for whom drug plasma concentration results (from at least 1 visit) are available. For the PK analysis population, talazoparib concentrations will be summarized descriptively by nominal time and talazoparib dose strength. Additionally, a subgroup of PK samples which meet pre-defined steady-state acceptance criteria (as detailed in the study SAP) will be summarized by nominal time and a within-patient average talazoparib steady state trough concentration will be listed by patient from this population.

9.1. Sample Size Determination

Current standard of care in TNBC consists of chemotherapy-based regimens. Published pCR rates vary greatly from 20% to 50%. Data is limited for neoadjuvant regimens in gBRCA positive TNBC where mostly retrospective subgroup analysis are available[54] with the best chemotherapy-based regimens showing ~50% pCR rates. Also, the investigator-initiated research study[23] in neoadjuvant gBRCA positive BC where patients were treated with talazoparib monotherapy shows ~50% pCR in a HER2 negative population. Similarly, patients with gBRCA mutated hormone receptor positive breast cancer had a pCR rate of 3/5 (60%) and a combined RCB 0+1 rate of 4/5 (80%).[22] Although based on a limited sample size, this promising pCR rate is substantially higher than that reported for patients with hormone receptor positive early breast cancer who receive chemotherapy and is similar to the pCR rates obtained by adding PARP inhibitors or carboplatin to conventional chemotherapy for the treatment of patients with early TNBC.[44-46] These results suggest talazoparib monotherapy may benefit the gBRCA mutated hormone receptor positive subgroup of patients with early breast cancer as well.

Approximately sixty patients will be enrolled in the study and treated with talazoparib 1 mg QD for 24 weeks followed by surgery. With a sample size of 60 patients, the two-sided 80% exact Blaker CI for the pCR rate would be at most 17% wide. If a pCR=50% is observed, the lower bound of the exact 80% CI would exclude 41%.

An interim futility analysis, designed based on Bayesian predictive probability (PP), will be conducted once 28 evaluable patients are assessed for pCR. The PP is the probability of concluding a positive result by the end of the trial based on the cumulative information in the current stage. The trial will be considered a success if the posterior probability that the true pCR rate exceeds 45% is ≥80%. Predictive probability <10% was set as the futility boundary and assumed a non-informative beta (1,1) prior. Once 28 evaluable patients are assessed for pCR, if 11 responses or less are observed, the predictive probability of the trial being successful at the full sample size is less than 10%, at which point the Sponsor would recommend stopping the study due to futility. If ≥12 responses are observed in the first 28 evaluable patients, the study will continue enrolling to 60 evaluable patients.

In the HR positive group after 6 evaluable patients have completed treatment and undergone surgery, the pCR rate will be assessed. If 2 patients achieve pCR out of the initial 6, then the posterior probability that the true pCR rate in the HR positive group is greater than 45% would be 28.9%, assuming a non- informative Beta (0.5,0.5) prior. Therefore, if 2 or more pCRs are observed, the HR positive subgroup will continue to enroll. If 1 or no pCRs are observed, then closing of the HR positive subgroup will be considered. In the event that

enrollment in the HR positive group is stopped, enrollment in the TNBC group will continue to a total of 60 patients. The evaluable population is the primary analysis population at the interim and final analysis. The intent-to-treat (ITT) population will include all patients who received at least one1 dose of talazoparib, regardless of whether or not they are considered evaluable.

9.2. Analysis of the Primary Endpoint

The primary study objective is to evaluate the pCR rate by independent central review (ICR) in the evaluable population.

pCR is defined as the absence of residual invasive cancer in the breast and axillary lymph nodes on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ie, ypT0/Tis ypN0 in the current AJCC staging system).

pCR rate by ICR is defined as the number and percentage of patients achieving pCR by independent central review after talazoparib treatment for 24 weeks, followed by surgery, among all patients in the evaluable population.

pCR rate by ICR will be analyzed at the time of the interim and final analyses and will be summarized along with the exact 80% and 95% CI.

pCR rate by ICR will also be summarized in the ITT population along with exact 80% and 95% CI. Patients who discontinue treatment or study prematurely, are lost to follow-up, withdraw consent, progress or die before pCR can be assessed by central review will be considered as non-responders in the ITT population analysis.

For all patients, study drug treatment should continue until completion of protocol assigned therapy, followed by surgery unless the patient is no longer clinically benefitting in the opinion of the investigator, there is unacceptable toxicity, withdrawal of consent, or death. Dosing interruptions are permitted for a period of 28 days to allow recovery from drug related toxicities. Patients who receive less than 80% of the prescribed talazoparib dose during the neoadjuvant treatment period will not be part of the evaluable population.

If a patient receives less than 80% of the protocol required treatment, undergoes surgery and achieves pCR by ICR, the patient will be counted as a responder in the ITT population, but will not be included in the evaluable population.

9.3. Analysis of Secondary Endpoints

The following efficacy parameters will be evaluated as secondary endpoints.

9.3.1. Pathological Complete Response by Investigator Review

pCR rate by investigator is defined as the number and percentage of patients achieving pCR by investigator review after talazoparib treatment for 24 weeks, followed by surgery, among all patients in the evaluable population pCR rate by investigator in the evaluable population will be analyzed at the time of the interim and final analyses and will be summarized along with the exact 95% CI.

pCR by investigator will also be summarized in the ITT population, along with the exact 95% CI. Patients who discontinue treatment or study prematurely, are lost to follow-up, withdraw consent, progress, or die before pCR can be assessed by investigator will be considered non-respondersin the ITT population analysis.

If a patient receives less than 80% of the protocol required treatment, undergoes surgery and achieves pCR by ICR, the patient will be counted as a responder in the ITT population, but will not be included in the evaluable population.

9.4. Ethical Conduct of the Study

This study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the following:

- International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002);
- ICH Guideline for Good Clinical Practice;
- US Code of Federal Regulations (CFR) sections that address clinical research studies, and/or other national and local regulations, as applicable;
- ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice (GGCP) E6 (ICH E6);
- The ethical principles established by the Declaration of Helsinki.

Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/EC/research ethics board (REB) and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the risks. The rights and welfare of the patients will be respected and subject participation continued as long as the Investigators conducting the study do not find the hazards to outweigh the potential benefits. Each patient, or his/her legally authorized representative will provide written, informed consent before any study-related tests or evaluations are performed.

9.4.1. Residual Cancer Burden

The residual cancer burden is a continuous index derived from the following: primary tumor dimensions; cellularity of the tumor bed; axillary nodal burden.

Residual cancer burden by ICR will be reported as a categorical variable with four classes (categories) RCB 0 (pCR), I (minimal RCB), II (moderate RCB), III (extensive RCB).

Number and percentage of patients for all 4 categories in the evaluable population will be reported along with exact 95% CI. The analysis of RCB by ICR will be conducted in the evaluable population.

9.4.2. Pathological Complete Response in Breast by Independent Central Review and Investigator

pCR in breast is defined as the absence of residual invasive cancer in the breast and axillary lymph nodes on hematoxylin and eosin evaluation of the complete resected breast specimen following completion of neoadjuvant therapy with talazoparib.

pCR rate in breast by ICR is defined as the number and percentage of patients achieving pCR in breast by independent central review after talazoparib treatment for 24 weeks, followed by surgery, among all patients in the evaluable population.

pCR rate in breast by investigator review is defined as the number and percentage of patients achieving pCR in breast by investigator review after talazoparib treatment for 24 weeks, followed by surgery, among all patients in the evaluable population.

pCR in breast rate will be summarized using descriptive statistics along with the exact 95% CI.

pCR in breast rate will also be summarized in the ITT population along with exact 95% CI Patients who discontinue treatment or study prematurely, are lost to follow-up, withdraw consent, progress or die before pCR in breast can be assessed, will be considered non-responders.

If a patient receives less than 80% of the protocol required treatment, undergoes surgery and achieves pCR in breast, the patient will be counted as a responder in the ITT population, but will not be included in the evaluable population.

9.4.3. Event-free Survival and Event-free Survival at 3 Years

EFS is defined as the time from surgery date to first documentation of local or distant recurrence or death or initiation of antineoplastic therapy before documentation of first relapse. Patients discontinuing study before documentation of first relapse or death, but after surgery will be censored observations for EFS. Additional details regarding censoring rules will be presented in the statistical analysis plan.

EFS at 3 years is defined as the probability of being event-free at 3 years using Kaplan Meier methods. The 95% CI for EFS at 3 years will be calculated using the Brookmeyer-Crowley method. The analysis of EFS at 3 years will be performed in the evaluable population.

9.4.4. Overall Survival and Overall Survival at 3 Years

OS is defined as the time from first dose of talazoparib to death due to any cause. Patients not known to have died at the time of the analysis will be right censored on the date they were last known to be alive before the analysis data cutoff date. Details on censoring conventions will be presented in the statistical analysis plan.

OS at 3 years is defined as the probability of being alive at 3 years after first dose of talazoparib using Kaplan-Meier methods. The 95% CI for OS at 3 years will be calculated using the Brookmeyer-Crowley method. The analysis of OS at 3 years will be performed in the evaluable and ITT population.

9.4.5. Time to Definitive Deterioration In Global Health Status/Qol Per European Organization For Research And Treatment Of Cancer Quality Of Life Questionnaire (EORTC QLQ-C30)

Time to definitive deterioration of patient-reported global health status/QoL (defined as >10-point decrease from baseline without any subsequent <10 point decrease) will be summarized using survival analysis methods. This will include Kaplan-Meier estimates of the median and 25th and 75th percentiles, 95% CI (based on the Brookmeyer-Crowley method), Kaplan-Meier plots will also be provided.

9.4.6. Time to Definitive Deterioration In Nausea And Vomiting Symptoms Per EORTC QLQ-C30

Time to definitive deterioration of patient-reported nausea and vomiting symptoms (defined as >10-point increase from baseline without any subsequent <10 point increase) will be summarized using survival analysis methods. This will include Kaplan-Meier estimates of the median and 25th and 75th percentiles, and 95% CI (based on the Brookmeyer-Crowley method). Kaplan-Meier plots will also be provided.

9.4.7. Change From Baseline In Global Health Status/Qol, Functioning, And Symptoms Per EORTC QLQ-C30 and EORTC QLQ BR-23[redacted]

A longitudinal mixed-effect model analyses will be used to assess change from baseline in global health status/QOL, functioning, and symptoms per EORTC QLQ-C30, EORTC QLQ BR-23[redacted]

9.4.8. Change From Baseline In Proportion Of Patients With Missed Expected Menstrual Period Versus Baseline And Proportion Of Patients With Deterioration In Nausea And Vomiting Symptoms

The proportion of female patients with missed expected menstrual period post baseline per PRO-CTCAE (vs proportion of patients with missed expected menstrual period at baseline); and proportion of patients with deterioration in nausea and vomiting symptoms (vs no deterioration) will be compared.

Deterioration in nausea and vomiting symptoms is defined as a ≥10 point increase from baseline for that specific time point.

Improvement in nausea and vomiting symptoms is defined as a ≥10 point decrease from baseline for that specific time point.

No change in nausea and vomiting symptoms would be defined as scores that do not satisfy both categories mentioned above.

9.5. Pharmacokinetic Analysis

The relationship between steady-state talazoparib trough concentrations with tumor response and/or safety findings after accounting for potential covariates may be evaluated. The results of any exploratory population PK/PD analysis may be reported separately from the clinical study report.

All patients treated with talazoparib for whom drug plasma results (from at least 1 visit) are available would be included in the PK analysis. Talazoparib concentrations will be summarized descriptively by nominal time and talazoparib dose strength. Additionally, a subgroup of PK samples which meet pre-defined steady-state acceptance criteria (as detailed in the study SAP) will be summarized by nominal time and a within-patient average talazoparib steady-state trough concentration will be listed by patient from this population.

CCI

[redacted]

CCI [redacted]

9.7. Exploratory Analysis

Subgroup analyses will be conducted as appropriate for pCR and RCB for the hormone receptor positive subgroup and the TNBC subgroup. The subgroup analyses will report exact confidence intervals for pCR by ICR and investigator. For RCB, the exact CIs will be calculated by ICR only.

9.8. Safety Analysis

All safety analyses will be performed using the safety population, defined as all patients who receive any amount of study drug. Drug exposure will be summarized using descriptive statistics. Treatment-emergent safety data will be collected from the first dose of study drug treatment through 28 days after the date of permanent discontinuation from study or before initiation of new antineoplastic or investigational therapy, whichever occurs first.

Adverse Events

The safety of talazoparib will be evaluated by the analysis of incidence of serious and non-serious adverse events, severity of adverse events, incidence of dose modifications and of permanent treatment discontinuation due to adverse events, and incidence of new clinically significant changes in clinical laboratory values and vital signs.

Adverse events will be coded to preferred term and system organ class using MedDRA and classified by severity using the CTCAE, version 4. The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and severity. Descriptive statistics will be used.

Analysis of Laboratory Results

Laboratory values will be classified by severity using the CTCAE, version 4. Laboratory shift tables of baseline to maximum post-baseline results to each subsequent visit will be produced as appropriate.

Analysis of Vital Signs/Physical Examination

Vital signs and physical examination findings will be summarized by visit using descriptive statistics.

9.9. Interim Analysis

One interim analysis will be performed to assess efficacy and safety after 28 evaluable patients complete talazoparib treatment 1 mg QD for 24 weeks, followed by surgery and assessment of pCR by ICR. The trial will be considered a success if the posterior probability that the true pCR rate exceeds 45% is ≥80%. At the interim, the criteria for futility are as follows: Once 28 evaluable patients are assessed for pCR, if 11 responses or less are observed, the predictive probability of a successful trial at the full sample size is less than

10%, at which point the investigator would recommend stopping the study due to futility. If ≥12 responses are observed in the first 28 evaluable patients, the study will continue enrolling to 60 patients.

In the HR positive group after 6 evaluable patients have completed treatment and undergone surgery, the pCR rate will be assessed. If 2 patients achieve pCR out of the initial 6, then the posterior probability that the true pCR rate in the HR positive group is greater than 45% would be 28.9%, assuming a non-informative Beta (0.5,0.5) prior. Therefore, if 2 or more pCRs are observed, the HR positive subgroup will continue to enroll. If 1 or no pCRs are observed, then closing of the HR positive subgroup will be considered.

Interim analysis results may be used for internal business decisions regarding future study planning. Additional analysis details will be documented in an interim analysis SAP or final SAP.

9.10. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the patient's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Patient Information and Consent

All parties will ensure protection of subject personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study patients. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient’s numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients’ personal data consistent with applicable privacy laws.

The informed consent documents and any patient recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (eg, decisionally-impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject, or the patient's legally acceptable representative, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each patient's signed consent document.

12.3. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the IP, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

End of trial is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application. Poor recruitment (recruiting less than the anticipated number in the CTA) is not a reason for premature termination but is considered a normal conclusion to the study.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or IP safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of talazoparib at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) as quickly as practical. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 24 weeks of the PCD for studies in pediatric populations.

PCD is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, “publication”) before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

16. REFERENCES

1. Almendro V, Jung Kim H, Cheng YK, et al. Genetic and phenotypic diversity in breast tumor metastases. Cancer Res 2014;74(5):1338–48.

2. Rivenbark AG, O'Connor SM, Coleman WB. Molecular and cellular heterogeneity in breast cancer: challenges for personalized medicine. Am J Pathol 2013;183(4):1113-24.

3. Campeau PM, Foulkes WD, Tischkowitz MD. Hereditary breast cancer: new genetic developments, new therapeutic avenues. Human Genetics 2008; 124(1):31 42.

4. Easton DF. How many more breast cancer predisposition genes are there? Breast Cancer Res 1999;1(1):14-7.

5. Halpern N, Sonnenblick A, Uziely B, et al. Oncotype Dx recurrence score among BRCA1/2 germline mutation carriers with hormone receptors positive breast cancer. Int J Cancer. 2017 May 1;140(9):2145-9.

6. Wong-Brown MW, Meldrum CJ, Carpenter JE et al. Prevalence of BRCA1 and BRCA2 germline mutations in patients with triple-negative breast cancer. Breast Cancer Res Treat 2015; 150(1):71-80.

7. Hartman AR, Kaldate RR, Sailer LM et al. Prevalence of BRCA mutations in an unselected population of triple-negative breast cancer. Cancer 2012; 118(11):2787-95.

8. Dent R, Trudeau M, Pritchard KI, et al. Triple negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007; 13(15):4429-34.

9. Byrski T, Gronwald J, Huzarski T et al. Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapty. J Clin Oncol 2010; 28(3):375-79.

10. Arun B, Bayraktar S, Liu DD et al. Response to neoadjuvant systemic therapy for breast cancer in BRCA mutation carriers and non-carriers: a single-institution experience. J Clin Oncol 2011; 29(28):3739-46.

11. Frasci G, Comella P, Rinaldo M, et al. Preoperative weekly cisplatin-epirubicin-paclitaxel with G-CSF support in triple-negative large operable breast cancer. Ann Oncol 2009; 20(7):1185-92.

12. Ford D, Easton DF, Bishop DT, et al. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet 1994; 343(8899):692-5.

13. Wooster R, Neuhausen SL, Mangion J, Quirk Y, Ford D, et al. Localization of a Breast Cancer Susceptibility Gene, BRCA2, to Chromosome 13q12 13. Science. 1994 265:2088–2090.

14. Scully R. Role of BRCA gene dysfunction in breast and ovarian cancer predisposition. Breast Cancer Res 2000; 2(5):324-30.

15. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010; 376:235–44.

16. Sandhu SK, Schelman WR, Wilding G, et al. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. Lancet Oncol 2013;14:882–92.

17. De Bono JS, Mina LA, Gonzalez M, et al. First-in-human trial of novel oral PARP inhibitor BMN 673 in patients with solid tumors. J Clin Oncol 2013; 31:2580.

18. Cheng H, Zhang Z, Borczuk A et al. PARP inhibition selectively increases sensitivity to cisplatin in ERCC1-low non-small cell lung cancer cells. Carcinogenesis 2013; 34(4): 739-49.

19. Davidson D, Wang Y, AloyZ R, et al. The PARP inhibitor ABT-888 synergizes irinotecan treatment of colon cancer cell lines. Invest New Drugs 2013; 31(2):461-8.

20. Robson M, Im S-A, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. New Eng J Med 2017; 377:523-33.

21. J Litton et al. EMBRACA: A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced germline BRCA mutation breast cancer. SABCS 2017 abstract.

22. Litton JK, Rugo HS, Johannes E et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med 2018; 379:753-63.

23. Litton JK, Scoggins M, Ramirez DL et al. A feasibility study of neoadjuvant talazoparib for early-stage breast cancer patients with a germline BRCA mutation demonstrates marked activity. NPJ Breast Cancer 2017.

24. Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. Biometrics 1982; 38(1):29 41.

25. Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. Cancer Res 2012; 72(21):5588 99.

26. Arnedos M, Bihan C, Delaloge S, et al. Triple negative breast cancer: are we making headway at least? Ther Adv Med Oncol 2012; 4(4):195 210.

27. American Cancer Society. Cancer facts & figures 2017 [Internet]. 2017 [cited 2017 Jun 27]. Available upon request from: https://www.cancer.org/content/dam/cancer org/research/cancer facts and statistics/annual cancer facts and figures/2017/cancer facts and figures 2017.pdf.

28. Robert M, Frenel JS, Gourmelon C, et al. Olaparib for the treatment of breast cancer. Expert Opin Investig Drugs 2017; 26(6):751 9.

29. Ismail Khan R, Bui MM. A review of triple negative breast cancer. Cancer Control 2010; 17(3):173 6.

30. Howlader N, Altekruse SF, Li CI et al US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 2014; 106(5):1-8.

31. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007; 25(11):1329-33.

32. Antoniou A, Pharoah PD, Narod S. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003; 72:1117-1130.

33. Atchley DP, Albarracin CT, Lopez A, et al. Clinical and pathologic characteristics of patients with BRCA positive and BRCA negative breast cancer. J Clin Oncol 2008; 26(26):4282 8.

34. Verhoog LC, Brekelmans CT, Seynaeve C, et al. Survival in hereditary breast cancer associated with germline mutations of BRCA2. J Clin Oncol 1999; 17(11):3396 402.

35. Rennert G, Bisland Naggan S, Barnett Griness O, et al. Clinical outcomes of breast cancer in carriers of BRCA1 and BRCA2 mutations. N Engl J Med 2007; 357(2):115 23.

36. Nicolini A, Carpi A, Rossi G. Cytokines in breast cancer. Cytokine Growth Factor Rev 2006; 17 (5): 325–37.

37. Bryant HE, Schultz N, Thomas HD. Specific killing of BRCA2 deficient tumours with inhibitors of poly (ADP ribose) polymerase. Nature 2005; 434(7035):913 7.

38. Chacón RD, Costanzo, MV. Triple-negative breast cancer. Breast Cancer Research 2010; 12(Suppl 2):S53.

39. von Minckwitz G, Loibl S, Untch M et al. Survival after neoadjuvant chemotherapy with or without bevacizumab or everolimus for HER2 negative primary breast cancer (GBG 44-GeparQuinto). Ann Oncol 2014; 25(12):2363-2372.

40. Gerratana L, Fanotto V, Bonotto M et al. Pattern of metastasis and outcome in patients with breast cancer. Clin Exp Metastasis 2015; 32(2):125-133.

41. Mavadatt M, Barrowdale D, Andrulis IL et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer Epidemiol Biomarkers Prev 2012; 21(1):134-147.

42. Teshome M, Hunt KK. Neoadjuvant therapy in the treatment of breast cancer. Surg Oncol Clin N Am 2014; 23(3):505 23.

43. Garber JE, Richardson A, Harris LN, et al. Neo-adjuvant cisplatin (CDDP) in "triple-negative" breast cancer (BC). In: 2006 San Antonio Breast Cancer Symposium; 14-17 Dec 2006; San Antonio, TX. 2006: Abstr 3074.

44. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol 2018;19(4):497-509.

45. Von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2 positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol. 2014 Jun;15(7):747-56.

46. Sikov WM, Berry DA, Perou CM et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol. 2015 Jan 1;33(1):13-21.

47. Turner NC, Telli ML, Rugo HS, et al. Final results of a phase 2 study of talazoparib (TALA) following platinum or multiple cytotoxic regimens in advanced breast cancer patients (pts) with germline BRCA1/2 mutations (ABRAZO). J Clin Oncol 2017; 35(15):1007.

48. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30(15):1796-804.

49. Foldi J, Mougalian S, Silber A, et al. Pathologic complete response (pCR) rates after neoadjuvant pertuzumab (P) and trastuzumab (H) administered concomitantly with weekly paclitaxel (T) and 5 fluorouracil/epirubicin/cyclophosphamide (FEC) chemotherapy for clinical stage I III HER2 positive breast cancer. J Clin Oncol 2017; 35(15):577.

50. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Pathological complete response in neoadjuvant treatment of high risk early stage breast cancer: use as an endpoint to support accelerated approval. In: Guidance for industry. Silver Spring, MD: Center for Drug Evaluation and Research; 2014: 21 pages.

51. Schreiber V, Dantzer F, Amé JC, de Murcia G. Poly(ADP ribose): novel functions for an old molecule. Nat Rev Mol Cell Biol. 2006 Jul;7(7):517 28.

52. Gibson BA, Kraus WL. New insights into the molecular and cellular functions of poly(ADP ribose) and PARPs. Nat Rev Mol Cell Biol. 2012 Jun 20;13(7):411 24.

53. Schreiber V, Amé JC, Dollé P, et al. Poly(ADP ribose) polymerase 2 (PARP 2) is required for efficient base excision DNA repair in association with PARP 1 and XRCC1. J Biol Chem 2002; 277(25):23028 36.

54. Amé JC, Rolli V, Schreiber V, et al. PARP 2, A novel mammalian DNA damage dependent poly(ADP ribose) polymerase. J Biol Chem 1999; 274(25):17860 8.

55. Johansson M. A human poly(ADP ribose) polymerase gene family (ADPRTL): cDNA cloning of two novel poly(ADP ribose) polymerase homologues. Genomics 1999; 57(3):442 5.

56. Hopkins TA, Shi Y, Rodriguez LE, et al. Mechanistic dissection of PARP1 trapping and the impact on in vivo tolerability and efficacy of PARP inhibitors. Mol Cancer Res 2015; 13(11):1465 77.

57. Murai J, Huang SY, Renaud A, et al. Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. Mol Cancer Ther 2014; 13(2):433 43.

58. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high grade serous or poorly differentiated ovarian carcinoma or triple negative breast cancer: a phase 2, multicentre, open label, non randomised study. Lancet Oncol 2011; 12(9):852 61.

59. Farmer H, McCabe N, Lord CJ. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005; 434(7035):917 21.

60. Curtin R, Presser S, Singer E. Changes in telephone survey nonresponse over the past quarter century. Public Opinion Quarterly 2005; 69:87–98.

61. Chambon P, Weill JD, Mandel P. Nicotinamide mononucleotide activation of new DNA-dependent polyadenylic acid synthesizing nuclear enzyme. Biochem Biophys Res Commun 1963; 11: 39–43.

62. Pommier Y, Sun Y, Huang SN, Nitiss, JL. Roles of eukaryotic topoisomerases in transcription, replication and genomic stability. Nat Rev Mol Cell Biol 2016; 17:703–721.

63. Lord CJ, Ashworth A. Mechanisms of resistance to therapies targeting BRCA-mutant cancers. Nature Medicine 2013; 19:1381-1388.

64. Clarke M, Collins R, Darby S et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 366: 2087–2106.

65. Shen S, Zhou Y, Xu Y et al. A multi-centre randomised trial comparing ultrasound vs mammography for screening breast cancer in high-risk Chinese women. Br J Cancer 2015; 112(6):998-1004.

66. Development Safety Update Report, Talazoparib (PF 06944076), 20 Jan 2017.

67. Osoba D, Bezjak A, Brundage M, Pater J. Evaluating health related quality of life in cancer clinical trials: The National Cancer Institute of Canada clinical trials group experience. J Clin Oncol 1998; 16:139-44.

68. Lindberg P, Netter P, Koller M et al. Breast cancer survivors` recollection of their quality of life: Identifying determinants of recall bias in a longitudinal population-based trial. PLoS One 2017; 12(2):1-14.

69. Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO CTCAE™); Frequently Asked Questions. [Internet; last updated 24 Feb 2017]. Available upon request from: https://healthcaredelivery.cancer.gov/pro ctcae/faqs.html.

Appendix 1. Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ABRAZO	A Phase 2, 2-Stage, 2-Cohort Study of Talazoparib (BMN 673), in Locally Advanced and/or Metastatic Breast Cancer Patients With BRCA Mutation (ABRAZO Study)
AC	cyclophosphamide
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
CCI	[redacted]
ANC	absolute neutrophil count
ASCO-CAP	American Society of Clinical Oncology-College of American Pathologists
AST	aspartate aminotransferase
CCI	[redacted]
Bcl-2	B-cell lymphoma 2
BCS	breast conserving surgery
BCRP	Breast cancer resistance protein
BCSR	breast conserving surgery rate
bd	twice daily
BICR	blinded independent central review
BioMarin	BioMarin Pharmaceutical, Inc. (San Rafael, CA); original holder of talazoparib IND
BMN 673	BioMarin Pharmaceutical, Inc. legacy compound number for talazoparib (also known as PF 06944076, MDV3800)
BRCA	breast cancer susceptibility gene
BRCA1	breast cancer susceptibility gene 1
BRCA2	breast cancer susceptibility gene 2
BRCA1/2	breast cancer susceptibility genes 1 and 2
BUN	blood urea nitrogen
cDNA	complementary DNA
CDx	Companion Diagnostics
CEP17	chromosome 17 polysomy
CFR	code of federal regulations
CI	confidence interval
CNS	central nervous system
CK	creatine kinase
CLCR	creatinine clearance
CL/F	apparent clearance
CLIA	Clinical Laboratory Improvement Amendments
CMF	cyclophosphamide, methotrexate, and fluorouracil

Abbreviation	Term
CR	complete response
CRF	case report form
CRR	clinical response rate
CRPR	C-reactive protein test
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CTSAE	Common Terminology for Serious Adverse Events
CCI [redacted]	[redacted]
Ctrough	trough concentrations
DCIS	ductal in situ carcinoma
DDR	DNA damage repair
DFS	disease-free survival
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DSB	double-strand break
DU	dispensable unit
DX	Diagnostics
EBC	early breast cancer
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EDP	exposure during pregnancy
EFS	event-free survival
EMBRACA	A Study Evaluating Talazoparib (BMN 673), a PARP Inhibitor, in Advanced and/or Metastatic Breast Cancer Patients With BRCA Mutation (EMBRACA Study)
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of Treatment
CCI [redacted]	[redacted]
ER	estrogen receptor
ESMO	European Society for Medical Oncology
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Adminstration
FSFV	first subject first visit
FSH	follicle-stimulating hormone

Abbreviation	Term
gBRCA	germline mutation of breast cancer susceptibility gene
GCP	Good Clinical Practice
GGCP	Guidelines for Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal tract
Hb	hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high density polyethylene
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HPMC	hydroxypropyl methylcellulose
hR	homologous recombination
hRD	homologous recombination defect
HR	heart rate
HRQL	health-related quality of life
HRT	hormonal replacement therapy
HRU	healthcare resource utilization
IB	investigator's brochure
ICH	International Council for Harmonisation
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
ICR	independent central review
ID	identification
IIR	investigator-initiated research
IND	investigational new drug application
INR	international normalized ratio
IHC	immunohistochemistry
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ISH	in situ hybridization
ITT	intent to treat analysis population
IUD	intrauterine device
IWR	interactive web response
IWRS	interactive web response system
IXRS	interactive voice and Web response system
LDH	lactate dehydrogenase
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
L/h	liters per hour
LSLV	last subject last visit

Abbreviation	Term
MDRD	modification of diet in renal disease
MDV3800	Legacy-Medivation, Inc. compound number for talazoparib (also known as PF 06944076, formerly BMN 673)
Medivation	Medivation, Inc., a wholly owned subsidiary of Pfizer Inc as of 28 September 2016 (in-licensed talazoparib from BioMarin on 06 October 2015)
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MnB	meningitis serogroup B
MRI	magnetic resonance imaging
N/A	not applicable
NSABP	National Surgical Adjuvant Breast and Bowel Project
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
p	probability value
PARP	poly(ADP-ribose) polymerase
PARP1	poly(ADP-ribose) polymerase 1
PARP2	poly(ADP-ribose) polymerase 2
PARPi	poly(ADP-ribose) polymerase inhibitor
pCR	pathological complete response
PCD	primary completion date
PD	pharmacodynamic(s)
PCT	physician's choice of treatment
PF-06944076	Pfizer Inc compound number for talazoparib (also known as MDV3800, formerly BMN 673)
PF-06944076-15	Pfizer Inc compound number for talazoparib tosylate
PFS	progression-free survival
PGx	pharmacogenomic(s)
PI	principal investigator
P-gp	permeability glycoprotein
PK	pharmacokinetic(s)
PP	predictive probability
PR	progesterone receptor
PRO	patient reported outcomes
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PT	prothrombin time
QD	once a day
QLQ	quality of life questionnaire
QLQ-BR23	Breast Cancer-Specific Quality of Life Questionnaire
QLQ-30	Quality of Life Questionnaire-Core 30
QoL	quality of life

Abbreviation	Term
RBC	red blood cells
RCB	residual cancer burden
REB	research ethics board
RECIST v1.1	revised response evaluation criteria in solid tumors
RNA	ribonucleic acid
RS	recurrence score
SAE	serious adverse event
SAP	statistical analysis plan
SMCC	with silicified microcrystalline cellulose
SOP	standard operating procedure
SRSD	single reference safety document
SSB	single-strand break
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TNBC	triple-negative breast cancer
TPC	treatment of physician's choice
ULN	upper limit of normal
US	United States
V/F	apparent volume of distribution
WBC	white blood cells
WCBP	women of childbearing potential

Definition of Terms:

Investigational Product (IP): "A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use" (from International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 [ICH E6]). The terms "IP" and "study drug" may be used interchangeably in the protocol.

Appendix 2. European Organisation for Research and Treatment of Cancer Quality-of-Life Core Questionnaire QLQ C30

We are interested in some things about you and your health. Please answer all of the questions yourself by selecting the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go to the next page

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please select the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

Appendix 3. European Organisation for Research and Treatment of Cancer Quality-of-Life Breast Cancer Module QLQ-BR23

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

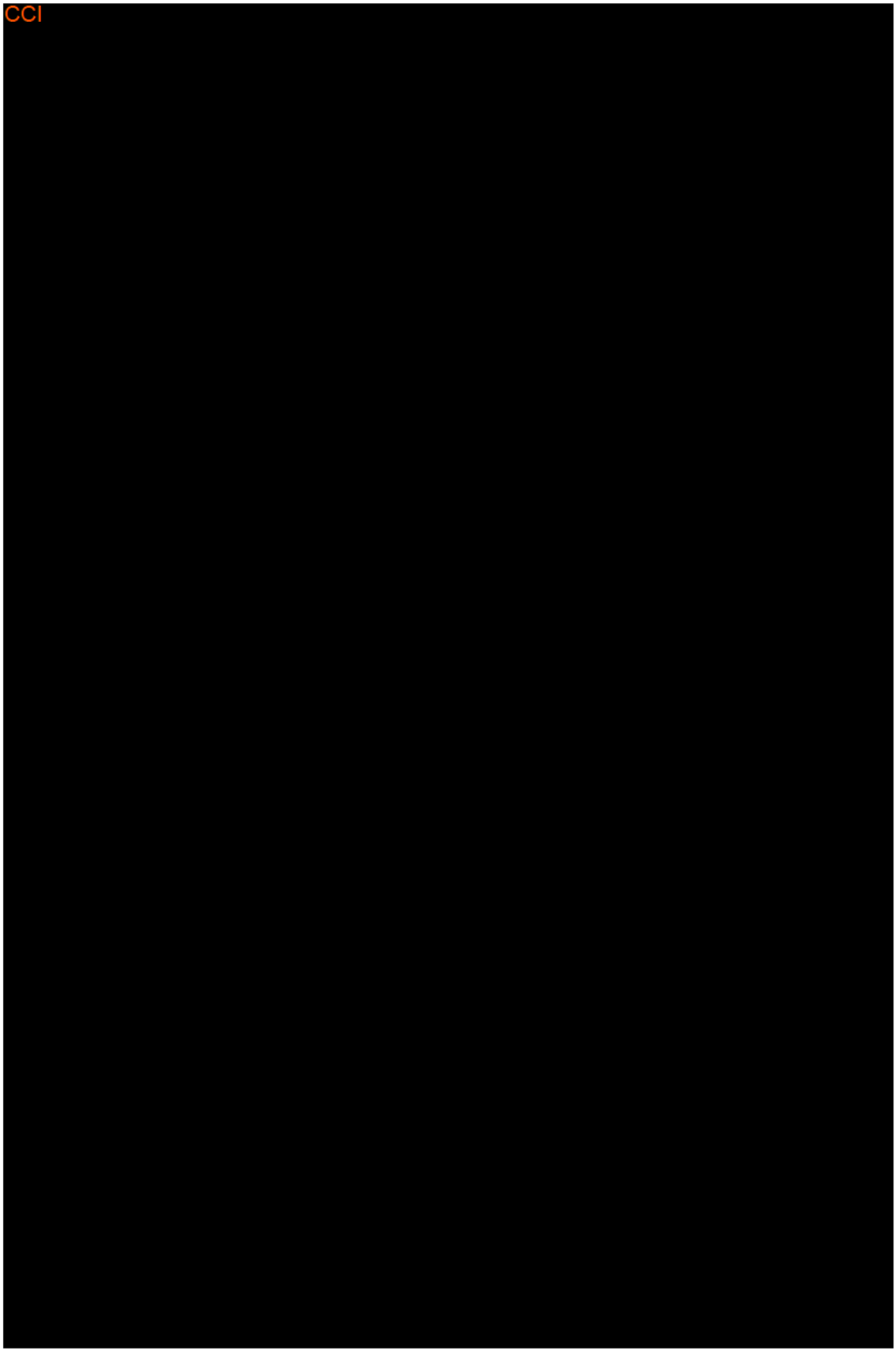
ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

CCI [redacted]

CCI [redacted]

CCI



Appendix 5. Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events

58. **PRO-CTCAE™ Symptom Term:** Missed expected menstrual period		
In the last 7 days, did you MISS AN EXPECTED MENSTRUAL PERIOD?		
O Yes	O No	O Not applicable