Non-Interventional Study Protocol

C3441053

Real-World Patient Characteristics, Treatment Patterns, and Clinical Outcomes Among Talazoparib-Treated Patients with HER2-Negative, Locally Advanced or Metastatic Breast Cancer and Germline BRCA1/2 Mutations: US Chart-Review

Statistical Analysis Plan (SAP)

Version: 1

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Date: 10-Sep-2021

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

N/A (first version)

2 INTRODUCTION

Note: in this document, any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

Breast cancer (BC) represents a major public health problem, with 284,200 new cases and 44,130 deaths estimated in the United States (US) during 2021.[1] Prognosis with metastatic BC is poor, with an estimated 5-year survival rate of approximately 28.1%.[2] Although the advent of novel therapeutic interventions such as immunotherapy and targeted agents have brought major strides in the treatment of locally advanced breast cancer not amenable to curative therapy or metastatic BC (ABC), *patients may continue to experience minimal or short-lived responses to these agents.[2] As such, the development and characterization of effective interventions are greatly needed in order to ensure patient-specific, appropriate, and tolerable treatment that achieves meaningful improvement in survival and quality of life. By increasing understanding of the true efficacy, safety, effectiveness, and treatment patterns of ABC-focused regimens in a broad, real-world (RW) patient population, RW studies can add tremendous value to this process.[3]*

BC is classified into 4 main disease subtypes based on hormone receptor (HR) status (i.e., estrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor receptor 2 (HER2) expression, including HR-positive/HER2-negative (luminal A), HR-negative/HER2-negative (triple-negative breast cancer [TNBC]), HR-positive/HER2-positive (luminal B), and HR-negative/HER2-positive (HER2-enriched).[4] Each subtype is associated with distinct disease features as well as treatment recommendations.[4,5] Treatment strategy may also be driven by mutation status of certain genes, including the BC susceptibility gene 1 or 2 (BRCA1 or BRCA2), in which mutations may render cells deficient in the repair of DNA double-strand breaks, thereby increasing reliance on poly (adenosine diphosphate–ribose) polymerase (PARP)-dependent, single-strand break repair mechanisms.[5-8] Germline BRCA1 or BRCA2 (gBRCA1/2) mutations account for approximately 5% of all BC cases, with prevalence of these mutations higher among those with HER2-negative disease.[9-11]

Talazoparib (TALZENNA®), which was approved by the US Food and Drug Administration (FDA) on October 16, 2018, is an orally available PARP inhibitor indicated for treatment of adult patients with HER2-negative ABC having gBRCA1/2 mutations.[12] This approval was based on the Phase 3 EMBRACA trial (NCT01945775), which demonstrated that, in comparison to single-agent chemotherapy of

the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine), talazoparib improved median progression-free survival (PFS) by approximately 3 months in adult patients diagnosed with HER2-negative ABC with gBRCA1/2 mutations (8.6 months vs 5.6 months [hazard ratio for disease progression or death, 0.54]; 95% confidence interval [CI], 0.41 to 0.71; P<0.001).[13,14] Additionally, the objective response rate (ORR) was 62.6% in the talazoparib arm versus 27.2% in the chemotherapy arm (odds ratio [OR], 5.0; 95% CI, 2.9 to 8.8; P<0.001).[13,14] Grade 3-4 hematologic adverse events (AEs) occurred in 55% of talazoparib-treated patients (primarily anemia) versus in 38% of chemotherapy-treated patients, whereas nonhematologic Grade 3 AEs occurred in 32% and 38% of patients, respectively.[13]

To date, there is no published information related to the characteristics, treatment patterns, and clinical outcomes of talazoparib-treated patients in the RW US setting. CCI [redacted]

CCI [redacted]

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CCI [redacted]

CCI [redacted]

2.1 STUDY DESIGN

This study consists of a retrospective, multi-site, patient-level medical chart-review of US adult ABC patients who initiated talazoparib on or after October 16, 2018 and were managed by participating providers from Cardinal Health's proprietary network, OPEN. Providers in OPEN who have previously indicated treating patients meeting the study selection criteria will be recruited and invited to participate. Additional providers in OPEN may be recruited to aid in patient recruitment.

Patient eligibility will be confirmed by the treating physician. Providers will abstract de-identified patient-level data necessary to achieve the research objectives into an eCRF. No protected health information (PHI), except for dates of diagnosis, treatment, and outcomes, will be collected. The patient's electronic health record (EHR) data will not be shared directly with Cardinal Health or Pfizer. All patient-level *data are secondary and will have been collected retrospectively from existing clinical data originally collected as part of routine care.* In addition, participating physicians will complete a survey aimed to capture physician and practice characteristics.

Data related to RW patient characteristics, treatment patterns, and clinical outcomes among talazoparib-treated patients will be captured and reported CCI [redacted]
CCI [redacted]

If sample size allows, clinical outcomes will also be reported for post-hoc analytic subgroups of interest only for the primary CCI [redacted] *Subgroups may include the following, to be determined once data collection is complete: patients with HR-positive/HER2-negative BC and patients with TNBC,* CCI [redacted]

CCI

Data collection is scheduled to begin in August 2021 and end in September 2021. The pre-index period will be variable and will encompass events and data occurring prior to the initiation of talazoparib treatment (e.g., initial breast cancer diagnosis, initial diagnosis of ABC, neoadjuvant/adjuvant therapy). Index date is defined as the date of initiation of talazoparib. The index period is defined as the period of time spanning the initiation of talazoparib on or after October 16, 2018 and the date of last follow-up. A minimum of 6 months follow-up after initiation of talazoparib is required for all patients, with the exception of patients who died within the follow-up period. The exact length of follow-up will be variable between patients (Figure 1).

3 FIGURE 1. STUDY PERIOD

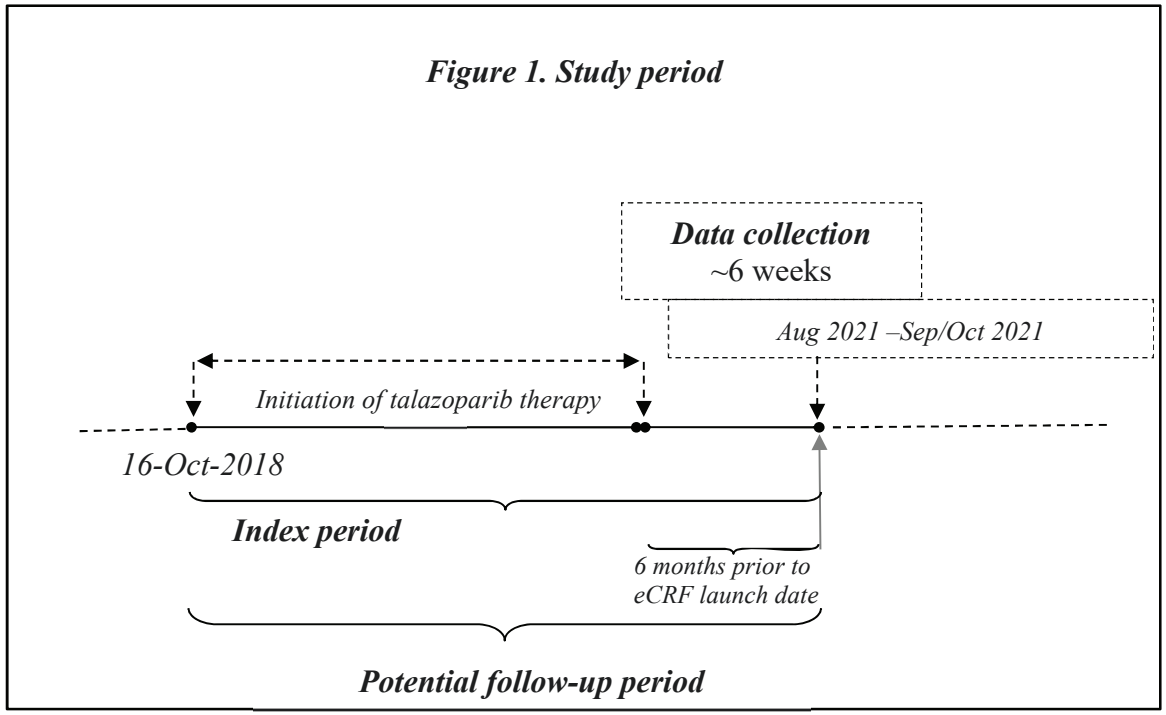

Table 1. Study Milestones

Milestone	***Planned date***
Completion of feasibility assessment	*01 March 2021*
Project kickoff	*10 March 2021*
Study protocol	*26 March 2021*
Study protocol finalization/approval	*23 June 2021*
Case report form (CRF)	*5 May 2021*
CRF finalization/approval	*28 June 2021*
Institutional review board (IRB) preparation/submission/approval	*08 July 2021*
eCRF programming & testing completion	*23 July 2021*
eCRF pre-test completion/eCRF finalized	*06 Aug 2021*
SAP & table shells	*16 Aug 2021*
SAP & table shells finalization/approval	*Q3 2021*
Start of data collection	*20 Aug 2021*
End of data collection	*Q3 2021*

Analytic/Clinical data quality review completion	*Q4 2021*
Data analysis completion	*Q4 2021*
Summary report	*Q4 2021*
Final study report	*Q4 2021*

Study population

Data will be captured and reported CCI *for* CCI CCI

One primary population of approximately 110 patients:

- *HER2-negative ABC patients with gBRCA1/2 mutations treated with talazoparib monotherapy initiated on or after October 16, 2018 and ≥18 years of age at initiation of talazoparib.*

All patients in the primary population will have had a minimum of 6 months follow-up time after initiation of talazoparib unless the patient died within this follow-up period. No patients will have participated in any BC clinical trial after initiation of talazoparib, been treated with a PARP inhibitor as neoadjuvant/adjuvant therapy, have unknown gBRCA1/2 status, or have been diagnosed with any other malignancy within the 5 years prior to data collection.

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CCI [redacted]

An estimated data exclusion rate of 3% following quality control (QC) processes is expected.

Data source

Data will be abstracted and entered into the eCRFs by patients' treating physicians within the OPEN. Recruitment will target the subset of OPEN providers who reported managing study eligible patients in the feasibility surveys and/or short chart-review. *Additional physicians from the OPEN may also be recruited to achieve the targeted patient numbers. These recruited providers who volunteer to participate in this study will identify patients meeting the study selection criteria through a series of screener questions. To be eligible for participation in this research study, a board-certified hematologist/oncologist must have treated or be treating at least 1 ABC patient meeting the eligibility criteria for the study, agree to participate in a study sponsored by Pfizer, and agree to complete and adhere to the Pfizer AE/*serious adverse event (SAE) *reporting protocols. Providers must also be able to participate in research monitored by a central IRB. No site-specific IRB approval will be sought, and providers requiring this approval will not be eligible.*

As of 2020, the OPEN community comprised more than 7,000 unique providers in oncology, hematology, and urology across the US who had participated in Cardinal Health internal market research, educational summits, industry-sponsored research, or whose practices had used the Cardinal Health proprietary point-of-care claims remittance software over the past 7 years. Of the providers, approximately 800 composed the RW research community, and 300 unique investigators have contributed patient-level data to retrospective chart abstraction research since 2016. OPEN is group purchasing organization (GPO)- and EHR- software agnostic. Providers are predominantly in community practices (>75%), ranging in size from solo practitioners to hospital systems, and participate in centralized IRB approval. Because OPEN is a provider-level (as opposed to site-based) community, CHSS can obtain large, representative samples of patients and collect detailed clinical data from their treating providers. Due to the purposive sampling that selects physicians and patients based on pre-specified selection criteria, however, this study may not be representative of all ABC patients treated with talazoparib or of all providers treating these types of patients.

Physicians will be asked to identify all eligible patients, report the total number of eligible patients, and chronologically select consecutive eligible patients, starting with the earliest eligible. Providers will submit a maximum of 10 eCRFs each (the maximum number of eCRFs per provider may be increased, if necessary, to achieve target patient numbers following pre-approval from Pfizer).

The source documents are the patient chart/medical record data housed within the EHRs and accessed by the participating providers. Data abstracted into the eCRFs must match those charts. To adhere to Pfizer's requirements for non-interventional studies (NIS) collecting data for patients treated with a Pfizer product, all providers who wish to participate will complete the required Pfizer pharmacovigilance (PV) training for reporting of AEs.

Through the chart-review approach, data elements contained in unstructured fields of the EHR (e.g., clinical progress notes, radiographic scans/reports, pathology reports) or those elements requiring a provider's interpretation (e.g., date of progression) can be collected. The eCRF is a custom data abstraction tool allowing the provider chart abstractor to input de-identified data directly from the patient EHR into a secure, web-based platform.

No source document verification can be conducted by CHSS; however, data QC, quality assurance (QA), and validation processes will be performed as described in Section 9.8 of the study protocol.

Treatment/cohort labels

During data reporting, the primary population of HER2-negative ABC patients with gBRCA1/2 mutations treated with talazoparib monotherapy will be labelled as "HER2- ABC g*BRCA1* CCI [redacted]

3.1 STUDY OBJECTIVES

***Primary objectives**:*

The following primary objectives will be assessed among adult patients with HER2-negative ABC with gBRCA1/2 mutations treated with talazoparib in the RW practice setting in the US:

1. *Describe demographic and clinical characteristics.*
2. *Describe patterns of treatment with talazoparib monotherapy* CCI [redacted]
   CCI [redacted]
3. *Describe RW clinical outcomes of talazoparib monotherapy-treated patients, including:*
   a. *Time to treatment failure (TTF) for talazoparib*
   b. *RW progression-free survival (rwPFS)*

   CCI [redacted]

   d. *RW overall response rate (rwORR)*

   CCI [redacted]

   f. *Time to chemotherapy administered following talazoparib*

Demographic and clinical characteristics and certain variables related to talazoparib treatment patterns and clinical outcomes of talazoparib-treated adult patients with HER2-negative ABC with g*BRCA1/2* mutations will be summarized using descriptive statistics: mean, standard deviation (SD), median, interquartile range (IQR), and minimum/maximum values will be calculated for continuous variables and for categorical data, counts and proportions will be calculated. Time-to-event endpoints such as TTF, rwPFS, CCI [redacted] CCI [redacted] and time to chemotherapy administered following talazoparib will be analyzed using the Kaplan-Meier (KM) method, accounting for right-censoring.

CCI [redacted]

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Data from primary CCI *population will be analyzed and reported separately* CCI

4 HYPOTHESES AND DECISION RULES

Due to the descriptive nature of this retrospective, observational study, no hypotheses have been specified a priori and no formal hypothesis testing will be performed.

5 ANALYSIS SETS/POPULATIONS

5.1 FULL ANALYSIS SET

Data will be captured and reported separately for the following 3 distinct cohorts of patients (cohorts will never be combined during analysis):

1. HER2- ABC g*BRCA1/2*m: HER2-negative ABC patients with g*BRCA1/2* mutations treated with talazoparib monotherapy (primary population)

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Inclusion criteria

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

- *≥18 years of age at initiation of talazoparib*
- *A minimum of 6 months follow-up time after initiation of talazoparib unless the patient died within this follow-up period*

*For HER2-**negative** patients with gBRCA1/2 mutations (population for primary analysis, approximately 110 patients):*

- *Diagnosed with HER2-negative ABC*
- *gBRCA1/2 mutation(s)*
- *Treatment with talazoparib monotherapy initiated on or after October 16, 2018*

CCI [redacted]

Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

- *Participation in any BC clinical trial after initiation of talazoparib*
- *Treatment with a PARP inhibitor as neoadjuvant/adjuvant therapy*
- *gBRCA1/2 or HER2 status unknown*
- *Diagnosis of any other malignancy, except carcinoma in situ or nonmelanoma skin cancer, within the 5 years prior to data collection*

5.2 SUBGROUPS

If sample size allows, clinical outcomes will also be reported for analytic subgroups of interest only for the HER2- ABC gBRCA1/2m *primary population* CCI *Subgroups may include the following, to be determined once data collection is complete: HR-positive/HER2-negative patients and patients with TNBC,* CCI CCI CCI *Additionally, stratification of patients by percentage of patients in their abstracting physician's practice with breast cancer may be conducted.*

6 ENDPOINTS AND COVARIATES

PHYSICIAN/PRACTICE CHARACTERISTICS

Table 2. Physician/practice characteristics (will be reported separately for CCI CCI HER2- ABC g*BRCA*1/2, CCI

Variable	Role	Operational definition
Primary Practice Setting	Cohort description	As collected:

		• By size: Solo practitioner, Small community practice (2-5 physicians), medium-sized community practice (6-10 physicians), large community practice (>10 physicians) • By type: Private community practice, academic medical center, community practice owned by an academic center, affiliated teaching hospital, Veteran's Affairs (VA)/military hospital/Department of Defense (DOD)
Urbanicity of practice	Cohort description	As collected: • Urban • Suburban • Rural
Region of practice	Cohort description	States will be collected and categorized into 4 US Census regions: • Northeast • Midwest • South • West
Specialty	Cohort description	• Medical oncology • Hematology/oncology • Gynecologial oncology
Years in practice	Cohort description	As collected: • Number of years
Percentage of patients in practice with breast cancer	Cohort description, may be used for	Estimate, per provider report

	patient stratification	
Total number of eligible patients	Cohort description	Estimate, per provider report
Number of ABC patients managed between 10/16/18 -[date of data collection launch minus180days]	Cohort description	Estimate, per provider report
Number of ABC patients managed between 10/16/18 -[date of data collection launch minus180days] treated with talazoparib	Cohort description	Estimate, per provider report
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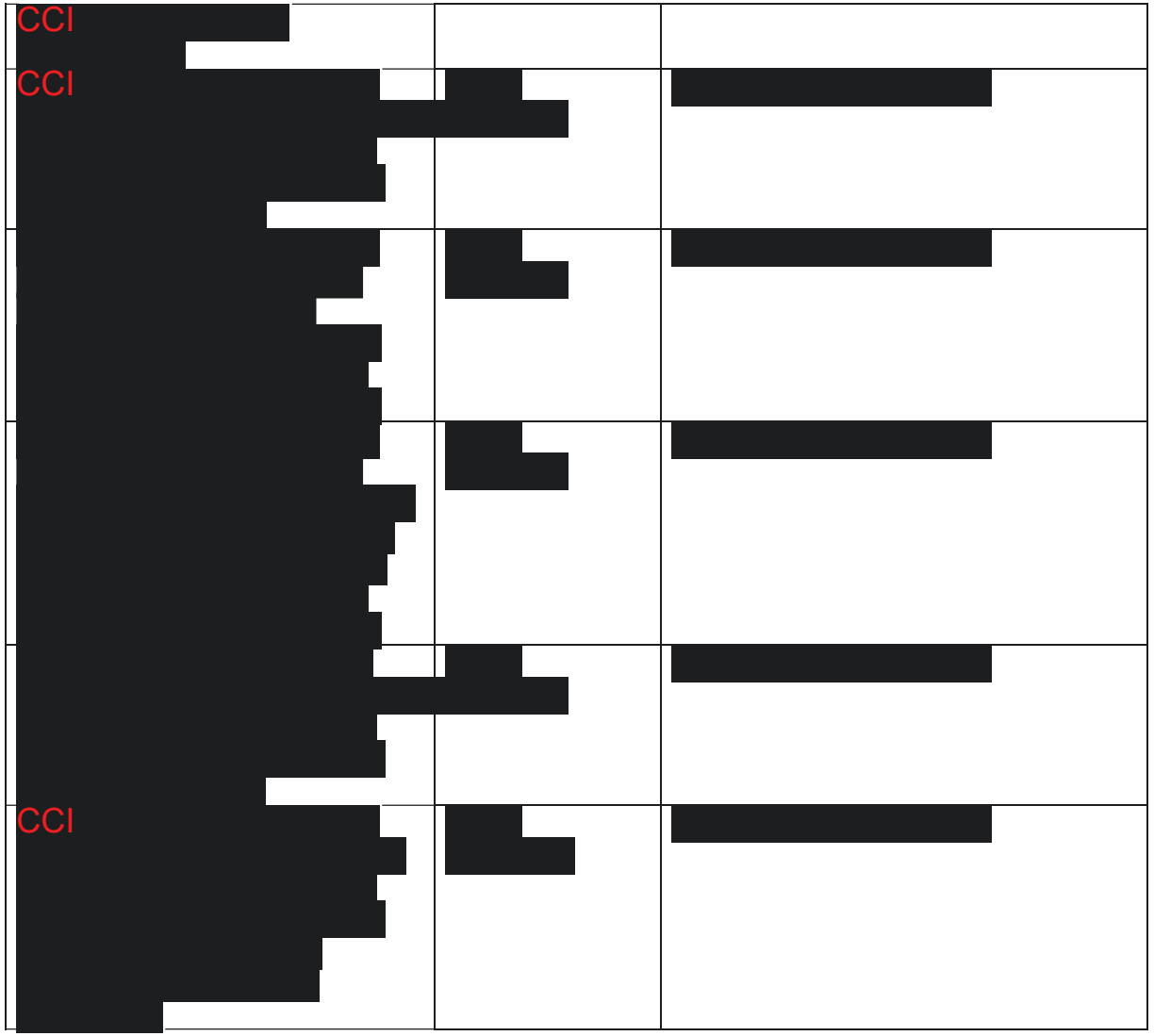
CCI		
CCI		
CCI		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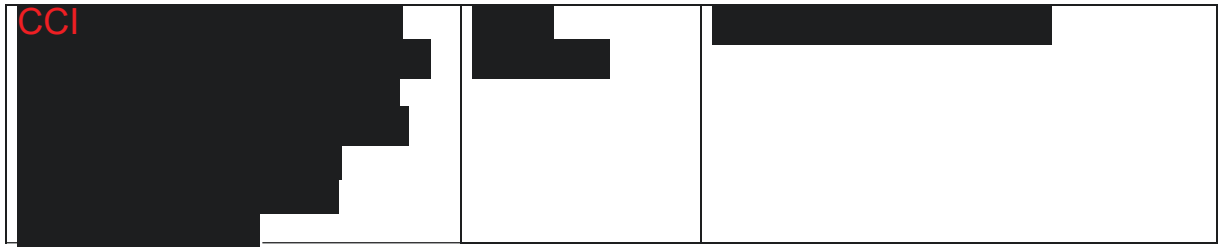

Table 3. Patient demographics

Variable	Role	Operational definition
Sex	Cohort description	As collected: • Female • Male
Year of birth	Cohort description	As collected: • YYYY Used to calculate: • Age at initial diagnosis of BC • Age at diagnosis of ABC • Age at initiation of talazoparib
Age at initial diagnosis of BC	Cohort description	Calculated from year of birth and date of initial diagnosis of BC

Age at diagnosis of ABC	Cohort description	Calculated from year of birth and date of initial diagnosis of ABC
Age at initiation of talazoparib	Cohort description, potential confounder	Calculated from year of birth and date of initiation of talazoparib
Payer	Cohort description	As collected: • Commercial • Medicare • Medicaid • Self-pay • Other (open text) • Unknown
Region of residence	Cohort description	As collected: • Northeast • Midwest • South • West
Race	Cohort description	As collected: • White • Asian • Black or African-American • Native Hawaiian or Other Pacific Islander • American Indian or Alaska Native

		• Other (open text) • Unknown
Ethnicity	Cohort description	As collected: • Hispanic/Latina/Latino • Non-Hispanic/Non-Latino/Non-Latina • Unknown
Ashkenazi jewish ancestry ethnicity	Cohort description	As collected: • Yes • No • Unknown

Table 4. Patient clinical characteristics

Variable	Role	Operational definition
Date of initial breast cancer diagnosis	Clinical characteristic	As collected: • MM/DD/YYYY Used to calculate: • Age at initial diagnosis of breast cancer • Time from initial BC diagnosis to ABC diagnosis
Date of diagnosis of ABC	Clinical characteristic	As collected: • MM/DD/YYYY Used to calculate: • Age at diagnosis of ABC • Time from initial BC diagnosis to ABC diagnosis
Time from initial BC diagnosis to ABC diagnosis	Clinical characteristic	Calculated as date of ABC diagnosis – date of initial BC diagnosis

American Joint Committee on Cancer (AJCC) stage at initial BC diagnosis	Clinical characteristic, potential confounder	As collected: • Stage I (Stage 1a, 1b) • Stage II • Stage IIIA • Stage IIIB • Stage IVA • Stage IVB • Unknown
AJCC stage at initiation of talazoparib	Clinical characteristic	As collected: • Stage IIIA • Stage IIIB • Stage IV
Molecular subtype of BC	Clinical characteristic, potential variable for stratification	As collected: • TNBC • HR+/HER2- CCI
Known family history for *BRCA*-related cancer	Clinical characteristic	As collected: • Breast • Ovarian • Fallopian tube(s) • Peritoneal • Prostate • Pancreatic • Gastric • Colon • No documented family history of *BRCA*-related cancers

Eastern Cooperative Oncology Group Performance Status (ECOG-PS) at baseline (prior to initiation of talazoparib)	Clinical characteristic, potential confounder	As collected: • 0 – Fully active; no restriction • 1 – Restricted in strenuous physical activities; fully ambulatory and able to carry out light work • 2 – Capable of all self-care but unable to carry out any work activities; up and about >50 percent of waking hours • 3 – Capable of only limited self-care; confined to bed or chair >50 percent of waking hours • 4 – Completely disabled; could not carry out any self-care; totally confined to bed or chair • Unknown
Karnofsky score at baseline (prior to initiation of talazoparib)	Clinical characteristic	As collected: • 100 - Normal; no complaints; no evidence of disease • 90 - Able to carry on normal activity; minor signs of symptoms of disease • 80 - Normal activity with effort; some sign or symptoms of disease • 70 - Cares for self; unable to carry on normal activity or do active work • 60 - Requires occasional assistance • 50 - Requires considerable assistance • 40 - Disabled; requires special assistance • 30 - Severely disabled

		• 20 - Very sick; requires active support treatment • 10 - Moribund • 0 - Unknown
Comorbidities	Clinical characteristic	As collected: • Acquired immunodeficiency syndrome (AIDS)/ human immunodefency virus (HIV) • Cerebrovascular disease • Chronic pulmonary disease • Congestive heart failure • Connective tissue disease • Dementia • Diabetes with chronic complications • Diabetes without chronic complications • Hemiplegia or paraplegia • Liver disease - mild • Liver disease – moderate or severe • Myocardial infarction • Other hematologic malignancy • Peptic ulcer disease • Peripheral vascular disease • Other (open text) • None of the above
Sites of metastases at the time of diagnosis of ABC	Clinical characteristic, may	As collected: • Adrenal gland

	be used for patient stratification	• Bone • Brain • Local lymph node(s) • Regional lymph node(s) • Distal lymph node(s) • Skin/soft tissue • Gastrointestinal system • Genitourinary system • Ovary • Gynecological system (excluding ovary) • Liver • Lung • Pleura, pericardial, and/or peritoneal cavity • Other (open text)
Sites of metastases at initiation of talazoparib initiation	Clinical characteristic, may be used for patient stratification	As collected: • Adrenal gland • Bone • Brain • Local lymph node(s) • Regional lymph node(s) • Distal lymph node(s) • Skin/soft tissue • Gastrointestinal system • Genitourinary system • Ovary

		• Gynecological system (excluding ovary) • Liver • Lung • Pleura, pericardial, and/or peritoneal cavity • Other (open text)
Visceral metastases at initiation of talazoparib	Clinical characteristic, may be used for patient stratification	Calculated based on whether metastases were reported in the adrenal gland; GI system; GU system; ovary, gynecological system; liver; lung; pleura, pericardial, and/or peritoneal cavity at the time of initiation of talazoparib: • Yes • No
Brain metastases at initiation of talazoparib	Clinical characteristic, may be used for patient stratification	Calculated based on whether metastases were reported in the brain: • Yes • No

Most recent g*BRCA1/2* mutation test (primary population CCI [redacted] CCI [redacted] CCI first somatic *BRCA1/2* mutation test, CCI [redacted]	Clinical characteristic/lab testing and results, may be used for patient stratification	As collected:
		• Panel type (multi gene, single gene, or unknown)
		• Lab
		  • AmbryGenetics
		  • ARUP Laboratories
		  • Caris Life Sciences

		• Color • FoundationOne • Guardant • Integrated Genetic • Invitae • Natera • NeoGenomics • Mayo Clinic Laboratories • Myriad Genetics • Pathway Genomics • Tempus • Ventana • Academic institution • Local lab • Physician's institution/affiliated hospital • Other (open text) • BRCA1 result • Positive (pathogenic) • Negative • Variant of uncertain clinical significance (VUS) • Variant suspected of deleterious/likely pathogenic • Genetic variant favor polymorphism • Other • BRCA2 result

		• Positive (pathogenic) • Negative • VUS • Variant suspected of deleterious/likely pathogenic • Genetic variant favor polymorphism • Other (open text)
Most recent ER expression analysis prior to initiation of talazoparib	Clinical characteristic/lab testing and results	As collected: • Test type (immunohistochemistry [IHC] or flouresence in situ hybridization [FISH]/ in situ hybridization [ISH]) • Result (positive or negative)
Most recent PR expression analysis prior to initiation of talazoparib	Clinical characteristic/lab testing and results	As collected: • Test type (IHC or FISH/ISH) • Result (positive or negative)
Most recent PD-L1 expression analysis prior to initiation of talazoparib	Clinical characteristic/lab testing and results	As collected: • Testing done and results available? (Tested, and results available, Tested, but results not available, Not tested, Unknown if prior testing completed) • If tested and results available: • Test type (IHC or other)

		• Result type (% immune cells [IC] or immune cells present [ICP], combined positive score [CPS], or other [open text]) • Result (open text)

Most recent *phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha* (*PIK3CA)* mutation analysis prior to initiation of talazoparib	Clinical characteristic/lab testing and results	As collected:
		• Testing done and results available? (Tested, and results available, Tested, but results not available, Not tested, Unknown if prior testing completed)
		• If tested and results available:
		  • Sample/test type (circulating tumor DNA or on tumor tissue)
		  • Result (detected or not detected

Most recent *estrogen receptor alpha/1* (*ESR1)* mutation analysis prior to initiation of talazoparib	Clinical characteristic/lab testing and results	As collected: • Testing done and results available? (Tested, and results available, Tested, but results not available, Not tested, Unknown if prior testing completed) • If tested and results available:

		• Sample/test type (circulating tumor DNA or on tumor tissue) • Result (detected or not detected)
Most recent HER2 expression analysis by IHC prior to initiation of talazoparib	Clinical characteristic/lab testing and results	As collected: • Result (0-1+ [negative]), 2+ [borderline], 3+ [positive])

6.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

Table 5. Patient treatment patterns and clinical outcomes

Variable	Role	Operational definition
TTF for talazoparib	Clinical outcome	Time from initiation of talazoparib to discontinuation for any reason, including disease progression, treatment toxicity, and death Patients still on therapy at last encounter will be censored at last encounter date

Adjuvant or neoadjuvant treatment for breast cancer	Treatment patterns, may be used for patient stratification	As collected:
		• Therapy type
		  • Neoadjuvant therapy
		  • Adjuvant therapy
		  • None of the above
		  • Unknown
		
		For neoadjuvant treatment:
		• Platinum-based chemotherapy

		• Non-platinum based chemotherapy
		• Hormonal therapy
		• HER2-directed therapy
		• Immunotherapy
		• None of the above, patient received other therapy not listed
		
		For adjuvant treatment:
		• Platinum-based chemotherapy
		  • Non-platinum based chemotherapy
		  • Hormonal therapy
		  • HER2-directed therapy
		  • Immunotherapy
		  • None of the above, patient received other therapy not listed

Systemic therapy for ABC received by line (up to 10 lines)	Treatment patterns, may be used for patient stratification	As collected: • Start and stop dates • A list of treatment regimens will be shown to providers; an option for "other, please specify" will be provided along with open text data entry for each line of therapy
Date of relapse or progression during each line of therapy	Clinical outcomes	As collected: • MM/DD/YYYY for each line


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		CCI [redacted]
Best response to talazoparib	Clinical outcomes	As collected: • Complete response • Partial response • Stable disease • Progressive disease • Not evaluable • Too early to tell (for patients still alive) • Unable to substantiate/lost to follow-up Used to calculate ORR
CCI [redacted]	[redacted]	[redacted]

		[redacted] CCI [redacted]
Patient vital status	Clinical outcomes	Date of death (MM/DD/YYYY), whether date of death is unknown How date of death was verified • Hospice notification • Family member notification • Routine follow-up communication • SSI • Other (open text) Cause of death • COVID-19 related • Disease progression • Unknown, data not available • Other
Date of last follow-up	Clinical outcomes	As collected:

		• MM/DD/YYYY To be used for censoring for endpoints including rwPFS, CCI TTF, CCI
Duration of follow-up	CCI clinical outcome	Calculated as date of last follow-up – date of talazoparib initiation
rwORR for talazoparib (among patients with disease response assessment)	Clinical outcome	Sum of complete and partial responses divided by all patients with reported disease response assessment
CCI		
Time to chemotherapy following talazoparib	Clinical outcome	Time from initiation of talazoparib to initiation of subsequent chemotherapy Patients who had not received chemotherapy at last encounter will be censored at last encounter date or date of death, whichever occurs first
rwPFS	Clinical outcome	Time from initiation of talazoparib to charted disease progression based on radiographic imaging or death from any cause, whichever occurs first Patients who discontinued talazoparib for a reason other than progression or death will be censored at talazoparib discontinuation date. Patients still

		receiving talazoparib at last encounter will be censored on date of last encounter.
CCI	[redacted]	[redacted]

6.2 SAFETY ENDPOINTS

N/A

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]


CCI

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

7.1.1 Analyses for Continuous Data

Distributions of continuous data will be summarized using descriptive statistics via measures of centrality and spread including mean, SD, median, IQR, and minimum/maximum values.

7.1.2 Analyses for Categorical Data/Binary Endpoints

Categorical data and binary endpoints will be summarized using descriptive statistics via counts and proportions.

6.1.3 Analyses for time-to-event endpoint analyses

Survival analyses for univariate time-to-event endpoints such as rwTTF, CCI and rwPFS, will be conducted using the Kaplan-Meier (KM) method, which accounts for right-censoring and enables the distribution of event occurrence to be based on continuous event times. KM survival curves, KM survival proportions at specified intervals, the number of events, and the number of patients censored will be provided. KM-estimated median values and 95% CIs around each point estimate will be reported when estimable.

6.1.4 Analyses for potential assessment of differences in odds of disease response and time-to-event clinical outcomes

Differences in the odds of disease response may be assessed (e.g., between subgroups) using logistic regression to calculate the OR and associated P-values and perform analyses adjusting for potential confounders (e.g., age at initiation of talazoparib, disease stage at initiation of talazoparib, ECOG-PS prior to talazoparib). If post-hoc analyses are performed, the log-rank test may be used to compare survival functions among subgroups for the primary analysis cohort. CCI [redacted] The comparison of means (medians where appropriate) and proportions across cohorts will be performed using t-tests (Wilcoxon where appropriate) and chi-square tests (Fisher exact where cell size is fewer than 5 patients).

7.2 STATISTICAL ANALYSES

All data collected and analyses performed are secondary. *Due to the descriptive nature of this retrospective, observational study, no hypotheses have been specified a priori and no formal hypothesis testing will be performed.* No data imputation will be conducted for missing data. For cases in which data flagged during QC processes cannot be validated, all data from the eCRF associated with unvalidated data will be excluded from analysis.

Primary CCI [redacted] *cohorts will be delineated and analyzed* CCI [redacted]

6.2.1 Statistical analyses for the HER2- ABC g*BRCA1/2*m primary analysis population

Baseline characteristics of adult HER2-negative ABC patients with g*BRCA1/2* mutations treated with talazoparib monotherapy in a RW practice setting in the US will be assessed in the primary analysis. Patient demographics and clinical characteristics will be summarized using descriptive statistics: mean, SD, median, IQR, and minimum/maximum values will be calculated for continuous variables while, counts and proportions will be calculated for categorical data and binary endpoints. This analysis will aim to address objective #1. Variables and endpoints related to patient demographic and clinical characteristics are described in Section 5 of the SAP (**Tables 3-4**).

Patterns of treatment with talazoparib monotherapy will be described for the primary population to address objective #2. Mean, SD, median, IQR, and minimum/maximum values will be calculated for continuous variables while, counts and proportions will be calculated for categorical data and binary endpoints. For time-to-event endpoints related to treatment patterns (e.g., TTF), analyses will be conducted using the KM method, accounting for right-censoring. *KM survival curves, KM survival proportions at specified intervals, the number of events, and the number of patients censored will be provided. KM-estimated median values and 95% CIs around each point estimate will be reported when estimable.* Variables and endpoints related to treatment patterns are described in Section 5.1 of the SAP (**Table 5**).

In order to address objective #3, clinical outcomes of talazoparib monotherapy-treated patients will be assessed. Univariate survival analysis will be conducted using the KM method as described in Section 6.1.3. *KM survival curves, KM survival proportions at specified intervals, the number of events, and the number of patients censored will be provided. KM-estimated median values and 95% CIs around each point estimate will be reported when estimable.* Variables and endpoints related to clinical outcomes are described in Section 5.1 of the SAP (**Table 5**).

Clinical outcomes will include the following:

- *rwTTF – time from initiation of talazoparib to discontinuation for any reason, including disease progression, treatment toxicity, and death*
    - *Patients still on therapy at last encounter will be censored at last encounter date*
- *rwPFS – time from initiation of talazoparib to disease progression based on radiographic imaging or death from any cause, whichever occurs first*

- *Patients who discontinued talazoparib for a reason other than progression or death will be censored at talazoparib discontinuation date. Patients still receiving talazoparib at last encounter will be censored on date of last encounter.*

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- *rwORR – sum of patients with reported complete and partial responses to talazoparib divided by all patients assessed for disease response*

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- *Time to chemotherapy – time from initiation of talazoparib to initiation of subsequent chemotherapy*

6.2.1.1 SubgroupCCI analyses for the HER2- ABC g*BRCA1/2*m primary analysis population

If sample size allows, clinical outcomes will also be reported for post-hoc analytic subgroups of interest only for the primary population
CCI

Subgroups may include the following, to be determined once data collection is complete:

- *HR-positive/HER2-negative BC*
- *TNBC*
- CCI
-

CCI

Additionally, patient characteristics and treatment patterns will be reported for the following subgroups of the HER2- ABC gBRCA1/2m primary analysis population:

- *HR-positive/HER2-negative BC*
- *TNBC*

If post-hoc analyses are performed, the log-rank test may be used to assess a difference in median time-to-event data among subgroups for the primary analysis cohort. To assess whether differences exist in the odds of disease response to treatment, the OR and associated P-values may be calculated, CCI CCI

6.2.1.2 Subgroup CCI analyses of physician characteristics

Physician/practice characteristics as depicted in Table 2 will be reported CCI for abstracting physicians who contributed to CCI of the cohorts in the final analysis: HER2- ABC g*BRCA*1/2, CCI

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7.2.1 Summary of Analyses

Table 7. Summary of analyses

Endpoint	HER2- ABC g*BRCA1/2*m primary population: Supports Objective #	CCI	Statistical method
Sex	1		Counts and proportions
Age at initial diagnosis of BC	1		Mean, SD, median, IQR, and minimum/maximum values
Age at diagnosis of ABC	1		Mean, SD, median, IQR, and minimum/maximum values

Time from initiation diagnosis of BC to ABC diagnosis	1	[redacted]	[redacted]	Mean, SD, median, IQR, and minimum/maximum values
Age at initiation of talazoparib	1	[redacted]	[redacted]	Mean, SD, median, IQR, and minimum/maximum values
Payer	1	[redacted]	[redacted]	Counts and proportions
Region of residence	1	[redacted]	[redacted]	Counts and proportions
Race	1	[redacted]	[redacted]	Counts and proportions
Ethnicity	1	[redacted]	[redacted]	Counts and proportions
Ashkenazi jewish ancestry ethnicity	1	[redacted]	[redacted]	Counts and proportions
AJCC stage at initial breast cancer diagnosis	1	[redacted]	[redacted]	Counts and proportions
AJCC stage at initiation of talazoparib	1	[redacted]	[redacted]	Counts and proportions
Molecular subtype of BC	1	[redacted]	[redacted]	Counts and proportions
Known family history for BRCA-related cancer	1	[redacted]	[redacted]	Counts and proportions
ECOG-PS at baseline (prior to initiation of talazoparib)	1	[redacted]	[redacted]	Counts and proportions
Karnofsky score at baseline (prior to initiation of talazoparib)	1	[redacted]	[redacted]	Counts and proportions
Comorbidities	1	[redacted]	[redacted]	Counts and proportions
Sites of metastases at the time of diagnosis of ABC	1	[redacted]	[redacted]	Counts and proportions
Sites of metastases at the time of talazoparib initiation	1	[redacted]	[redacted]	Counts and proportions
Visceral metastases at initiation of talazoparib	1	[redacted]	[redacted]	Counts and proportions
Brain metastases at initiation of talazoparib	1	[redacted]	[redacted]	Counts and proportions
Most recent *gBRCA1/2* mutation test (primary population [redacted]	1	[redacted]	[redacted]	Counts and proportions

Most recent ER expression analysis prior to initiation of talazoparib (test type, result)	1	[redacted]	[redacted]	Test type, result: Counts and proportions
Most recent PR expression analysis prior to initiation of talazoparib (test type, result)	1	[redacted]	[redacted]	Test type, result: Counts and proportions
Most recent PD-L1 expression analysis prior to initiation of talazoparib (whether testing was done and results available, test type, result type, result)	1	[redacted]	[redacted]	Counts and proportions
Most recent *PIK3CA* mutation analysis prior to initiation of talazoparib (whether testing was done and results available,sample/ test type, result)	1	[redacted]	[redacted]	Whether testing was done and results available,sample/ test type, result: Counts and proportions
Most recent *ESR1* mutation analysis prior to initiation of talazoparib (whether testing was done and results available,sample/ test type, result)	1	[redacted]	[redacted]	Whether testing was done and results available,sample/ test type, result: Counts and proportions
Most recent HER2 expression analysis by IHC prior to initiation of talazoparib (result)	1	[redacted]	[redacted]	Result: Counts and proportions
Adjuvant or neoadjuvant treatment for breast cancer	2	[redacted]	[redacted]	Counts and proportions
Systemic therapy for ABC received by line (up to 10 lines)	2	[redacted]	[redacted]	Counts and proportions
Number of lines of therapy for ABC prior to talazoparib	2	[redacted]	[redacted]	Counts and proportions
CCI [redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]

CCI	[redacted]	[redacted]	[redacted]	CCI
Best response to talazoparib	2	[redacted]	[redacted]	Counts and proportions
CCI	[redacted]	[redacted]	[redacted]	CCI
Duration of follow-up	2	[redacted]	[redacted]	Mean, SD, median, IQR, and minimum/maximum values
rwORR for talazoparib (among patients with disease response assessment)	2	[redacted]	[redacted]	Counts and proportions
CCI	[redacted]	[redacted]	[redacted]	CCI
TTF for talazoparib	3	[redacted]	[redacted]	KM-estimated median, 95% CI, KM curve
Time to chemotherapy following talazoparib	3	[redacted]	[redacted]	KM-estimated median, 95% CI, KM curve
rwPFS	3	[redacted]	[redacted]	KM-estimated median, 95% CI, KM curve
CCI	[redacted]	[redacted]	[redacted]	CCI

8 REFERENCES

Table 8. Table of abbreviations

Abbreviation	Definition
ABC	Locally advanced breast cancer not amenable to curative therapy or metastatic breast cancer
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer

Abbreviation	Definition
BC	Breast cancer
BRCA1	Breast cancer susceptibility gene 1
BRCA2	Breast cancer susceptibility gene 2
CDK	Cyclin-dependent kinase
CHSS	Cardinal Health Specialty Solutions
CI	Confidence interval
CNS	Central nervous system
CPS	Combined positive score
CRF	Case report form
DOD	Department of defense
ECOG-PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic case report form
EHR	Electronic health record
ER	Estrogen receptor
ESA	Erythropoiesis-stimulating agent

Abbreviation	Definition
ESR1	Estrogen receptor alpha/1
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
gBRCA1/2	Germline BRCA1 or 2
G-CSF	Granulocyte-colony stimulating factor
GPO	Group purchasing organization
HER2	Human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	Hormone receptor
IC	Immune cells
ICP	Immune cells present
IHC	Immunohistochemistry
IQR	Interquartile range
IRB	Institutional review board
ISH	In situ hybridization

Abbreviation	Definition
KM	Kaplan-Meier
KPS	Karnofsky performance status
NIS	Non-interventional
NIS	Non-interventional study
OPEN	Oncology Provider Extended Network
OR	Odds ratio
ORR	Objective response rate
CCI [redacted]	[redacted]
PARP	Poly(adenosine diphosphate–ribose) polymerase
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PR	Progesterone receptor
PH	Proportional hazards
PHI	Protected health information

Abbreviation	Definition
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PV	Pharmacovigilance
QA	Quality assurance
QC	Quality control
RW	Real-world
CCI	[redacted]
rwORR	Real-world overall response rate
rwPFS	Real-world progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
TNBC	Triple-negative breast cancer
TTF	Time to treatment failure
US	United States
VA	Veteran's Affairs

Abbreviation	Definition
VUS	Variant of uncertain clinical signficance

9 LIST OF TABLES AND TABLE SHELLS

Tables

Figures

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10 REFERENCES

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11 APPENDICES